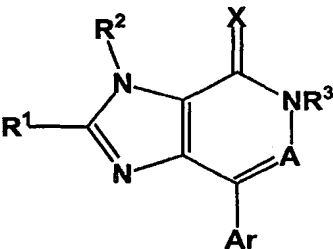




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C07D 471/02, 487/02, A61K 31/4188,</b> <b>A61P 25/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/39127</b> <b>(43) International Publication Date:</b> 6 July 2000 (06.07.00)
<b>(21) International Application Number:</b> PCT/US99/31325 <b>(22) International Filing Date:</b> 30 December 1999 (30.12.99) <b>(30) Priority Data:</b> 60/114,188                      30 December 1998 (30.12.98)      US <b>(71) Applicant:</b> DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilmington, DE 19807 (US). <b>(72) Inventors:</b> GILLIGAN, Paul, Joseph; 2629 Pennington Drive, Wilmington, DE 19810 (US). BAKTHAVATCHALAM, Rajagopal; 125 Berry Drive, Wilmington, DE 19808 (US). <b>(74) Agent:</b> RUBIN, Kenneth, B.; Du Pont Pharmaceuticals Com- pany, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		<b>(81) Designated States:</b> AL, AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> 1H-IMIDAZO[4,5-D]PYRIDAZIN-7-ONES, 3H-IMIDAZO[4,5-C]PYRIDIN-4-ONES AND CORRESPONDING THIONES AS CORTICOTROPIN RELEASING FACTOR (CRF) RECEPTOR LIGANDS <div style="text-align: center; margin: 20px 0;">  <div style="display: flex; justify-content: space-between; align-items: center; width: 100%;"> <div></div> <div>(I)</div> </div> </div> <b>(57) Abstract</b> <p>Corticotropin releasing factor (CRF) antagonists of formula (I), and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AL</b>	Albania	<b>ES</b>	Spain	<b>LS</b>	Lesotho	<b>SI</b>	Slovenia
<b>AM</b>	Armenia	<b>FI</b>	Finland	<b>LT</b>	Lithuania	<b>SK</b>	Slovakia
<b>AT</b>	Austria	<b>FR</b>	France	<b>LU</b>	Luxembourg	<b>SN</b>	Senegal
<b>AU</b>	Australia	<b>GA</b>	Gabon	<b>LV</b>	Latvia	<b>SZ</b>	Swaziland
<b>AZ</b>	Azerbaijan	<b>GB</b>	United Kingdom	<b>MC</b>	Monaco	<b>TD</b>	Chad
<b>BA</b>	Bosnia and Herzegovina	<b>GE</b>	Georgia	<b>MD</b>	Republic of Moldova	<b>TG</b>	Togo
<b>BB</b>	Barbados	<b>GH</b>	Ghana	<b>MG</b>	Madagascar	<b>TJ</b>	Tajikistan
<b>BE</b>	Belgium	<b>GN</b>	Guinea	<b>MK</b>	The former Yugoslav Republic of Macedonia	<b>TM</b>	Turkmenistan
<b>BF</b>	Burkina Faso	<b>GR</b>	Greece	<b>ML</b>	Mali	<b>TR</b>	Turkey
<b>BG</b>	Bulgaria	<b>HU</b>	Hungary	<b>MN</b>	Mongolia	<b>TT</b>	Trinidad and Tobago
<b>BJ</b>	Benin	<b>IE</b>	Ireland	<b>MR</b>	Mauritania	<b>UA</b>	Ukraine
<b>BR</b>	Brazil	<b>IL</b>	Israel	<b>MW</b>	Malawi	<b>UG</b>	Uganda
<b>BY</b>	Belarus	<b>IS</b>	Iceland	<b>MX</b>	Mexico	<b>US</b>	United States of America
<b>CA</b>	Canada	<b>IT</b>	Italy	<b>NE</b>	Niger	<b>UZ</b>	Uzbekistan
<b>CF</b>	Central African Republic	<b>JP</b>	Japan	<b>NL</b>	Netherlands	<b>VN</b>	Viet Nam
<b>CG</b>	Congo	<b>KE</b>	Kenya	<b>NO</b>	Norway	<b>YU</b>	Yugoslavia
<b>CH</b>	Switzerland	<b>KG</b>	Kyrgyzstan	<b>NZ</b>	New Zealand	<b>ZW</b>	Zimbabwe
<b>CI</b>	Côte d'Ivoire	<b>KP</b>	Democratic People's Republic of Korea	<b>PL</b>	Poland		
<b>CM</b>	Cameroon	<b>KR</b>	Republic of Korea	<b>PT</b>	Portugal		
<b>CN</b>	China	<b>KZ</b>	Kazakstan	<b>RO</b>	Romania		
<b>CU</b>	Cuba	<b>LC</b>	Saint Lucia	<b>RU</b>	Russian Federation		
<b>CZ</b>	Czech Republic	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DE</b>	Germany	<b>LK</b>	Sri Lanka	<b>SE</b>	Sweden		
<b>DK</b>	Denmark	<b>LR</b>	Liberia	<b>SG</b>	Singapore		
<b>EE</b>	Estonia						

TITLE

1H-Imidazo[4,5-d]pyridazin-7-ones, 3H-Imidazo-  
[4,5-c]pyridin-4-ones and Corresponding Thiones as  
5 Corticotropin releasing Factor (CRF) Receptor Ligands

FIELD OF THE INVENTION

This invention relates a treatment of  
10 psychiatric disorders and neurological diseases  
including major depression, anxiety-related  
disorders, post-traumatic stress disorder,  
supranuclear palsy and feeding disorders as well as  
treatment of immunological, cardiovascular or heart-  
15 related diseases and colonic hypersensitivity  
associated with psychopathological disturbance and  
stress, by administration of certain 1H-imidazo[4,5-  
d]pyridazin-7-ones, 3H-imidazo-[4,5-c]pyridin-4-ones  
and corresponding thiones.

20

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to  
as CRF), a 41 amino acid peptide, is the primary  
25 physiological regulator of proopiomelanocortin(POMC) -  
derived peptide secretion from the anterior pituitary  
gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)*  
80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)].  
In addition to its endocrine role at the pituitary gland,  
30 immunohistochemical localization of CRF has demonstrated  
that the hormone has a broad extrahypothalamic  
distribution in the central nervous system and produces a  
wide spectrum of autonomic, electrophysiological and  
behavioral effects consistent with a neurotransmitter or  
35 neuromodulator role in brain [W. Vale et al., *Rec. Prog.*

Horm. Res. 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional



support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)].

There is preliminary evidence that tricyclic

- 5 antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces  
10 anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83

- 15 (1986)]. Preliminary studies using the putative CRF receptor antagonist  $\alpha$ -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces  $\alpha$ -anxiolytic-like effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in  
25 these disorders. Chlordiazepoxide attenuates the  $\alpha$ -anxiogenic effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al.,  
30 *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142)

enhanced the actions of CRF [K.T. Britton et al.,  
*Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which  
the standard anxiolytics and antidepressants produce  
5 their therapeutic effects remain to be elucidated. It  
has been hypothesized however, that they are involved in  
the suppression of the CRF hypersecretion that is  
observed in these disorders. Of particular interest is  
that preliminary studies examining the effects of a CRF  
10 receptor antagonist ( $\alpha$ -helical CRF<sub>9-41</sub>) in a variety of  
behavioral paradigms have demonstrated that the CRF  
antagonist produces anxiolytic-like effects  
qualitatively similar to the benzodiazepines [for review  
see G.F. Koob and K.T. Britton, In: *Corticotropin-*  
15 *Releasing Factor: Basic and Clinical Studies of a*  
*Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC  
Press p221 (1990)].

Several publications describe corticotropin  
releasing factor antagonist compounds and their use to  
20 treat psychiatric disorders and neurological diseases.  
Examples of such publications include DuPont Merck PCT  
application US94/11050 , Pfizer WO 95/33750, Pfizer WO  
95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

## 25 SUMMARY OF THE INVENTION

In accordance with one aspect, the present  
invention provides novel compounds, pharmaceutical  
compositions and methods which may be used in the  
30 treatment of affective disorder, anxiety, depression,  
irritable bowel syndrome, post-traumatic stress disorder,  
supranuclear palsy, immune suppression, Alzheimer's  
disease, gastrointestinal disease, anorexia nervosa or  
other feeding disorder, drug or alcohol withdrawal  
35 symptoms, drug addiction, inflammatory disorder,

fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders

5 such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood

10 disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human

15 immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and

20 post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate

25 antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including

30 hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in

35 chickens, sheering stress in sheep or human-animal

interaction related stress in dogs); muscular spasms;  
urinary incontinence; senile dementia of the Alzheimer's  
type; multiinfarct dementia; amyotrophic lateral  
sclerosis; chemical dependencies and addictions (e.g.,  
5 dependencies on alcohol, cocaine, heroin,  
benzodiazepines, or other drugs); drug and alcohol  
withdrawal symptoms; osteoporosis; psychosocial dwarfism  
and hypoglycemia in a mammal.

10       The present invention provides novel compounds  
which bind to corticotropin releasing factor receptors,  
thereby altering the anxiogenic effects of CRF secretion.  
The compounds of the present invention are useful for the  
treatment of psychiatric disorders and neurological  
15 diseases, anxiety-related disorders, post-traumatic  
stress disorder, supranuclear palsy and feeding disorders  
as well as treatment of immunological, cardiovascular or  
heart-related diseases and colonic hypersensitivity  
associated with psychopathological disturbance and stress  
20 in a mammal.

According to another aspect, the present invention  
provides novel compounds of Formula (1) (described below)  
which are useful as antagonists of the corticotropin  
25 releasing factor. The compounds of the present invention  
exhibit activity as corticotropin releasing factor  
antagonists and appear to suppress CRF hypersecretion.  
The present invention also includes pharmaceutical  
compositions containing such compounds of Formula (1) and  
30 methods of using such compounds for the suppression of  
CRF hypersecretion, and/or for the treatment of  
anxiogenic disorders.

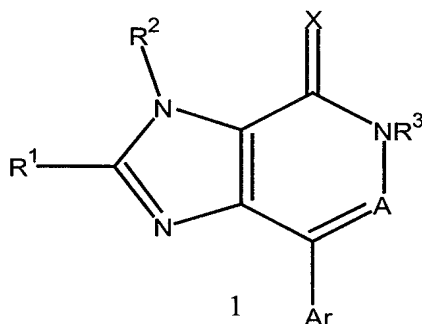
According to yet another aspect of the invention,  
35 the compounds provided by this invention (and especially

labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

5

#### DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises novel compounds of Formula (1) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. This invention comprises compounds of Formula (1):



15

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

20

X is O or S;

A = N or CR<sup>9</sup>;

25

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-

benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R<sup>4</sup> groups and each Ar is attached via an unsaturated carbon atom;

5 R<sup>1</sup> is independently selected at each occurrence from H, C<sub>1</sub>-C<sub>4</sub>†alkyl, C<sub>2</sub>-C<sub>4</sub>†alkenyl, C<sub>2</sub>-C<sub>4</sub>†alkynyl, halo, CN, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, C<sub>1</sub>-C<sub>12</sub> hydroxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>10</sub> cyanoalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, NR<sup>9</sup>R<sup>10</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sup>9</sup>R<sup>10</sup>,  
 10 NR<sup>9</sup>COR<sup>10</sup>, OR<sup>11</sup>, SH or S(O)<sub>n</sub>R<sup>12</sup>;

R<sup>2</sup> is selected from:

-H, aryl, heteroaryl and heterocyclyl,  
 or

15 -C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-C<sub>8</sub>†cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents  
 20 independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, C<sub>1</sub>-<sub>6</sub> alkyloxyC<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>3</sub>-<sub>6</sub> alkynyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>,  
 25 N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and heterocyclyl;

R<sup>3</sup> is selected from:

-H, aryl, heteroaryl and heterocyclyl,

30 or C<sub>1</sub>-C<sub>4</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†alkenyl, C<sub>3</sub>-C<sub>6</sub>†alkynyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl,  
 35

cyano,  $OR^{15}$ , SH,  $S(O)_nR^{13}$ ,  $COR^{15}$ ,  $CO_2R^{15}$ ,  $OC(O)R^{13}$ ,  $NR^8COR^{15}$ ,  $N(COR^{15})_2$ ,  $NR^8CONR^{16}R^{15}$ ,  $NR^8CO_2R^{13}$ ,  $NR^{16}R^{15}$ ,  $CONR^{16}R^{15}$ , aryl, heteroaryl and heterocyclyl;

5

$R^4$  is independently selected at each occurrence from:  $C_1$ - $C_{10}$ alkyl,  $C_2$ - $C_{10}$ alkenyl,  $C_2$ - $C_{10}$ alkynyl,  $C_3$ - $C_6$  cycloalkyl,  $C_4$ - $C_{12}$ cycloalkylalkyl,  $NO_2$ , halo, CN,  $C_1$ - $C_4$ haloalkyl,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CO_2R^7$ ,  $COR^7$ ,  
 10  $OR^7$ ,  $CONR^6R^7$ ,  $CO(NOR^9)R^7$ ,  $CO_2R^7$ , or  $S(O)_nR^7$ , where each such  $C_1$ - $C_{10}$ alkyl,  $C_2$ - $C_{10}$ alkenyl,  $C_2$ - $C_{10}$ alkynyl,  $C_3$ - $C_6$  cycloalkyl and  $C_4$ - $C_{12}$ cycloalkylalkyl are optionally substituted with  
 15 1 to 3 substituents independently selected at each occurrence from  $C_1$ - $C_4$  alkyl,  $NO_2$ , halo, CN,  $NR^6R^7$ ,  $NR^6COR^7$ ,  $NR^6CO_2R^7$ ,  $COR^7$ ,  $OR^7$ ,  $CONR^6R^7$ ,  $CO_2R^7$ ,  $CO(NOR^9)R^7$ , or  $S(O)_nR^7$ ;

$R^6$  and  $R^7$  are independently selected at each occurrence  
 20 from:  
 -H,  
 - $C_1$ - $C_{10}$  alkyl,  $C_3$ - $C_{10}$  alkenyl,  $C_3$ - $C_{10}$  alkynyl,  $C_1$ - $C_{10}$  haloalkyl with 1-10 halogens,  $C_2$ - $C_8$  alkoxyalkyl,  $C_3$ - $C_6$ cycloalkyl,  $C_4$ -  
 25  $C_{12}$ cycloalkylalkyl,  $C_5$ - $C_{10}$  cycloalkenyl, or  $C_6$ - $C_{14}$  cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from  
 30  $C_1$ - $C_6$ alkyl,  $C_3$ - $C_6$ cycloalkyl, halo,  $C_1$ - $C_4$ haloalkyl, cyano,  $OR^{15}$ , SH,  $S(O)_nR^{13}$ ,  $COR^{15}$ ,  $CO_2R^{15}$ ,  $OC(O)R^{13}$ ,  $NR^8COR^{15}$ ,  $N(COR^{15})_2$ ,  $NR^8CONR^{16}R^{15}$ ,  $NR^8CO_2R^{13}$ ,  $NR^{16}R^{15}$ ,  $CONR^{16}R^{15}$ , aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl,  
heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl);

5 alternatively, NR<sup>6</sup>R<sup>7</sup> is piperidine, pyrrolidine,  
piperazine, N-methylpiperazine, morpholine or  
thiomorpholine, each optionally substituted with 1-3 C<sub>1</sub>-  
C<sub>4</sub> alkyl groups;

10 R<sup>8</sup> is independently selected at each occurrence from H or  
C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted by halogen, C<sub>1</sub>-  
C<sub>4</sub> alkoxy or C<sub>1</sub>-C<sub>4</sub> halo-alkoxy (1 to 4 halogens);

R<sup>9</sup> and R<sup>10</sup> are independently selected at each occurrence  
15 from H, C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

R<sup>11</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

20 R<sup>12</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> haloalkyl;

R<sup>13</sup> is selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub>  
alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, C<sub>4</sub>-  
C<sub>12</sub>†cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
25 heteroaryl or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;

R<sup>15</sup> and R<sup>16</sup> are independently selected at each occurrence  
from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>16</sub>  
cycloalkylalkyl, except that for S(O)<sub>n</sub>R<sup>15</sup>, R<sup>15</sup>  
30 cannot be H;

aryl is phenyl or naphthyl, each optionally substituted  
with 1 to 5 substituents independently selected at  
each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl,  
35 halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>15</sup>,



COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>,  
NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>16</sup>R<sup>15</sup>, and CONR<sup>16</sup>R<sup>15</sup>;

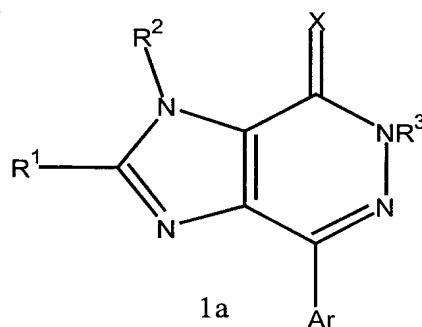
heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl,  
5       pyranyl, quinolinyl, isoquinolinyl, thienyl,  
imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,  
benzofuranyl, benzothienyl, benzothiazolyl,  
isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or  
2,3-dihydrobenzofuranyl, each being optionally  
10       substituted with 1 to 5 substituents independently  
selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-  
C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>,  
SH, S(O)<sub>n</sub>R<sup>15</sup>, -COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>,  
N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>16</sup>R<sup>15</sup>, and  
15       CONR<sup>16</sup>R<sup>15</sup>;

heterocyclyl is saturated or partially saturated  
heteroaryl, optionally substituted with 1 to 5  
substituents independently selected at each  
20       occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl,  
halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>15</sup>,  
COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>,  
NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, and CONR<sup>16</sup>R<sup>15</sup>;

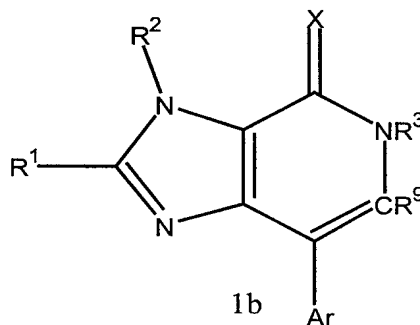
25       n is independently at each occurrence 0, 1 or 2.

[2] Preferred compounds of the above invention also  
include compounds of Formula (1) and isomers thereof,  
stereoisomeric forms thereof, or mixtures of  
30       stereoisomeric forms thereof, and pharmaceutically  
acceptable salt or pro-drug forms thereof wherein Ar is  
phenyl or pyridyl, each optionally substituted with 1 to  
4 R<sup>4</sup> substituents.

[3] More preferred compounds of the above invention also include compounds and isomers thereof of formula 1 wherein A is equal to nitrogen (formula 1a), stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and  
5 pharmaceutically acceptable salt or pro-drug forms thereof.



[4] The present invention also relates to compounds,  
10 compositions, and stereoisomeric forms, pharmaceutical salts or pro-drugs thereof wherein, in a compound of formula 1, A is equal to CR<sup>9</sup> (formula 1b):



15 [5] More preferred compounds of the invention include those compounds of formula 1 wherein X is equal to oxygen.

[6] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms  
20 thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof

wherein Ar is phenyl or pyridyl and each Ar is optionally substituted with 1 to 3 R<sup>4</sup> substituents.

[7] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R<sup>2</sup> is:

10 - C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-C<sub>8</sub>†cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and heterocyclyl.

[8] More preferred compounds also include those compounds of formula 1 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected at each position from zC<sub>1-6</sub> alkyl.

[9] The present invention comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections,

hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by  
5 antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula (1) with the variables as recited above.

10

The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above and a pharmaceutically acceptable carrier.

15

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric  
20 isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such  
25 as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically  
30 indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is  
35 propyl, Bu is butyl. The prefix "n" means a straight

chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(S)" means the S enantiomer and the prefix "(R)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentylmethoxycarbonyl and adamantylmethoxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a

stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

30

#### Syntheses

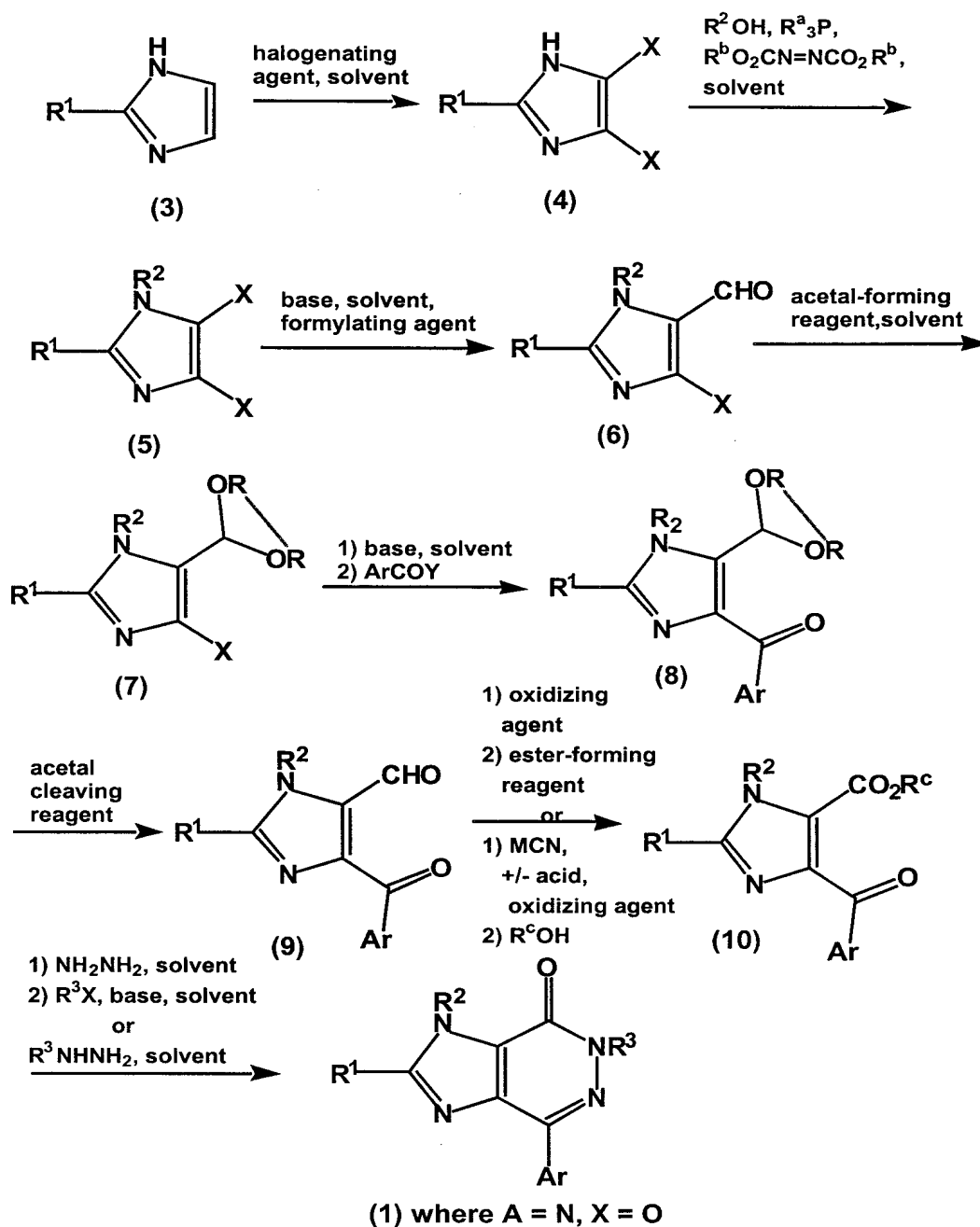
Some compounds of Formula (1) where X = O and A = N, may be prepared from intermediate compounds of Formula (3) using the procedures outlined in Scheme 1. Compounds of Formula (3) may be treated with a halogenating agent in the

presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (4) (where X is halogen). Halogenating agents include, but are not limited to, Br<sub>2</sub>, Cl<sub>2</sub>, I<sub>2</sub>, N-bromosuccinimide, N-iodosuccinimide or N-chlorosuccinimide. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 150°C. The resulting intermediates (4) may then be reacted with alcohols R<sup>2</sup>OH, where R<sup>2</sup> is defined above, in the presence of phosphines R<sup>a</sup><sub>3</sub>P (where R<sup>a</sup> is lower alkyl, phenyl or substituted phenyl or furyl) and an azodicarboxylate ester R<sup>b</sup>O<sub>2</sub>CN=NCO<sub>2</sub>R<sup>b</sup> (where R<sup>b</sup> is lower alkyl) in an inert solvent at temperatures ranging from -80°C to 150°C. Inert solvents may include, but are not limited to, polyethers (preferably 1,2-dimethoxyethane), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane) or aromatic hydrocarbons (preferably benzene or toluene). The choices of phosphine, solvent or azodicarboxylate ester are known to those skilled in the art as described by O. Mitsunobu (Synthesis, 1 [1981]). Intermediates (5) are treated with a base or an alkali metal in an inert solvent and then reacted with formylating agents



YCHO. Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group. Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkaline earth metal halides (e.g. methylmagnesium bromide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide) and alkali metal bis(trialkylsilyl)-amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Scheme 1



The resulting aldehydes (6) may be converted to  
 5    acetals (7) by treatment with an acetal-forming reagent in  
 the presence or absence of an acid in an inert solvent. The  
 dotted line between the R groups means that they may or may

not be connected. Acetal-forming reagents may be alcohols ROH, where R is lower alkyl, diols HOR---ROH where R---R is lower alkylene, or orthoesters HC(OR)<sub>3</sub> where R is lower alkyl. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C.

Acetals (7) may then be reacted with a base in an inert solvent, followed by treatment with a compound ArCOY (where Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group) to afford intermediates (8). Bases may include, but are not limited to, alkyl lithiums, alkali metal dialkylamides (preferably lithium di-isopropylamide) or alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane or aromatic hydrocarbons (preferably benzene or toluene). Intermediates (8) may then be converted to

compounds of Formula (9) by treatment with an acetal-cleaving reagent in an inert solvent. Acetal-cleaving reagents may include, but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, alkanolic acids, alkylsulfonic acids, substituted phenylsulfonic acids, camphorsulfonic acid or haloalkylsulfonic acids. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

The keto-aldehydes (9) may be converted to esters (10) by treatment with an oxidizing agent in an inert solvent to give a carboxylic acid, followed by treatment with an ester-forming reagent. Oxidizing agents include transition metal oxides, such as  $\text{CrO}_3$  or  $\text{KMnO}_4$  (with or without a buffering agent such as  $\text{NaH}_2\text{PO}_4$ ), pyridinium dichromate or pyridine- $\text{SO}_3$  complex. Inert solvents include water, alkanones (e.g. acetone), aqueous solutions of  $\text{HCl}$  or  $\text{H}_2\text{SO}_4$ , or N,N-dialkylformamides. Ester-forming reagents include but are not limited to alcohols  $\text{R}^{\text{C}}\text{OH}$ , where  $\text{R}^{\text{C}}$  is lower alkyl, or orthoesters  $\text{HC}(\text{OR}^{\text{C}})_3$  or combinations of a halogenating reagent and an alcohol  $\text{R}^{\text{C}}\text{OH}$  used sequentially or in the same reaction. Halogenating agents include, but are not limited to,  $\text{POCl}_3$ ,  $(\text{COCl})_2$ ,  $\text{SOCl}_2$ , N-halosuccinimides,  $\text{PCl}_3$ ,  $\text{PCl}_5$  or  $\text{PBr}_3$ . Inert solvents for the halogenation include, but are not limited to, aromatic hydrocarbons (preferably benzene or toluene), aromatic amines (e.g. pyridine) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably

dichloromethane). Preferred reaction temperatures range from 0°C to 150°C.

- Alternatively, aldehydes (9) may be reacted with a compound MCN, where M is H, alkali metal or
- 5 tetraalkylammonium moiety, in an inert solvent, treated with an oxidizing agent and reacted with alcohols R<sup>C</sup>OH where R<sup>C</sup> is lower alkyl. Oxidizing include, but are not limited to, transition metal oxides, such as CrO<sub>3</sub> or MnO<sub>2</sub>, pyridine-chromium complexes, such as CrO<sub>3</sub>.C<sub>5</sub>H<sub>5</sub>N, pyridinium
- 10 dichromate or pyridinium chlorochromate or an oxalylchloride-dimethylsulfoxide-triethylamine reagent system, commonly called the Swern oxidation system (D. Swern et al., J. Organic. Chem., 43, 2480-2482 (1978)). Inert solvents of the oxidation include, but are not limited to,
- 15 halocarbons of 1 to 6 carbons, preferably dichloromethane or 1,2-dichloroethane, lower alkyl alcohols, preferably ethanol or methanol, or lower alkanolic acids, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or combinations thereof.
- 20 Esters (10) may then be converted to compounds of Formula (1) where X = O and A = N by one of two methods. Esters (10) may be reacted with hydrazine or its hydrate in an inert solvent, then treated with an alkylating agent in the presence or absence of a base in an inert solvent to
- 25 provide compounds of Formula (1) where X is O and A = N. Phase transfer catalysts (e.g. tetra-alkylammonium halides or hydroxides) may be optionally employed for the alkylations. Alternatively, esters (10) may be reacted with compounds of Formula R<sup>3</sup>NHNH<sub>2</sub> (where R<sup>3</sup> is defined above) in
- 30 the presence or absence of a base in an inert solvent. Alkylating agents are compounds of the formula R<sup>3</sup>Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not
- 35 limited to, alkali metal carbonates, alkali metal

- bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine).
- 10 Inert solvents may include, but are not limited to, water, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-
- 15 dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably
- 20 dichloromethane) or combinations thereof. Preferred reaction temperatures range from -80°C to 100°C.

- Compounds of Formula (1) where A = N and X = O may be converted to compounds of Formula (1) where A = N and X = S according to the procedures outlined in Scheme 2. Compounds
- 25 of Formula (1) where A = N, X = O and R<sup>3</sup> = H may be converted to compounds of Formula (1) where A = N, X = S and R<sup>3</sup> = H by treatment with a thiocarbonyl-forming reagent in an inert solvent. Thiocarbonyl-forming reagents include but are not limited to, P<sub>2</sub>S<sub>5</sub> or Lawesson's reagent. Inert
- 30 solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-
- 35 dialkylacetamides (preferably dimethylacetamide), cyclic

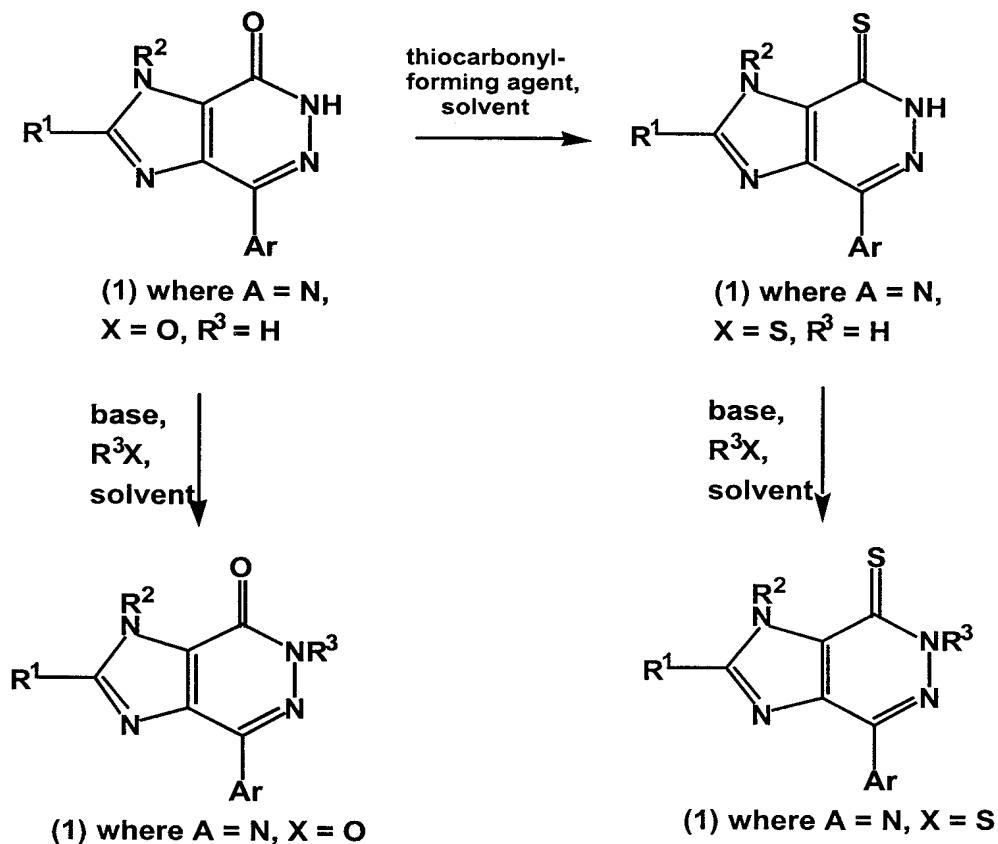
- amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 160°C. These intermediates may then be converted to compounds of Formula (1) where A = N, X = S and R<sup>3</sup> is not equal to H by treatment with an alkylating agent in the presence or absence of a base in an inert solvent.
- 10 Alkylating agents are compounds of the formula R<sup>3</sup>Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 150°C.
- 35 Alternatively, Compounds of Formula (1) where A = N, X = O

and  $R^3$  is not equal to H may be converted to compounds of Formula (1) where  $A = N$ ,  $X = S$  and  $R^3$  is not equal to H by treatment with a thiocarbonyl-forming reagent in an inert solvent. The reagent and inert solvent are defined above.

5



Scheme 2



- 5 Compounds of Formula (1) where A = CR<sup>9</sup> may be prepared from esters (10) by the methods outlined in Scheme 3. Esters (10) may be treated with phosphonium salts of the formula R<sup>d</sup><sub>3</sub>PCH R<sup>9</sup>OR<sup>f</sup>+ X<sup>-</sup> where R<sup>d</sup> is phenyl or substituted phenyl or phosphonates (R<sup>e</sup>O)<sub>2</sub>P(O)CHR<sup>9</sup>OR<sup>f</sup> in the presence of
- 10 a base in an inert solvent to give enol ethers (12). Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali
- 15 metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium

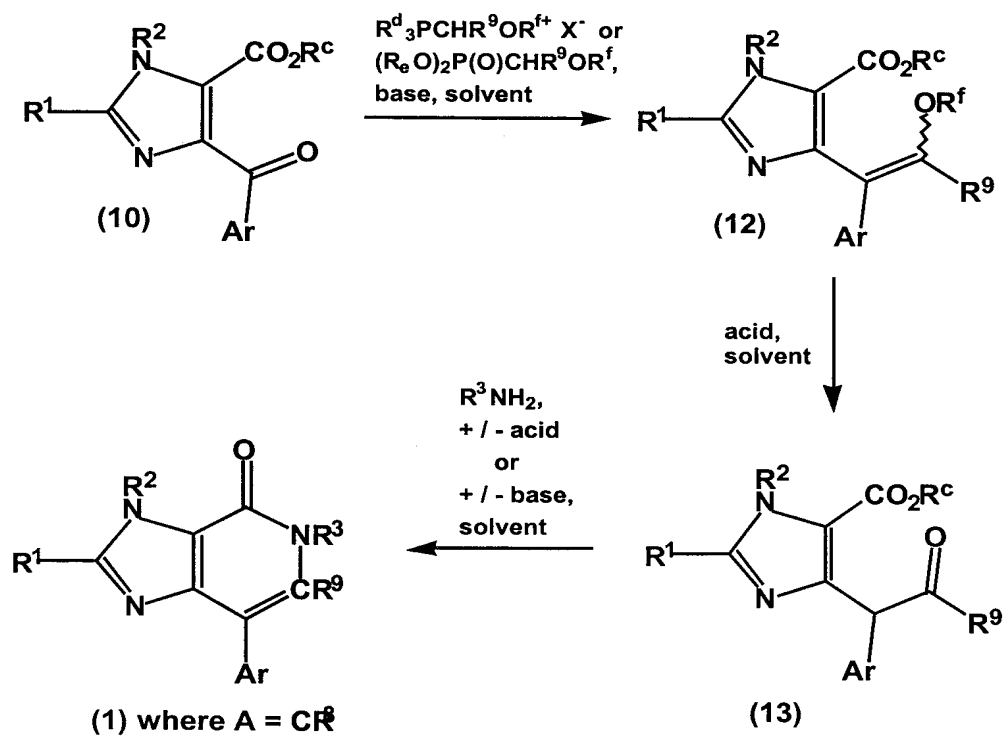
bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether) or cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane). Intermediates (12) may be hydrolyzed to give intermediates (13) in the presence of an acid in an inert solvent. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C.

Aldehydes (13) may be treated with amines  $R^3NH_2$  to generate compounds of Formula (1) where  $A = CR^8$  in the presence or absence of an acid or base in an inert solvent. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to

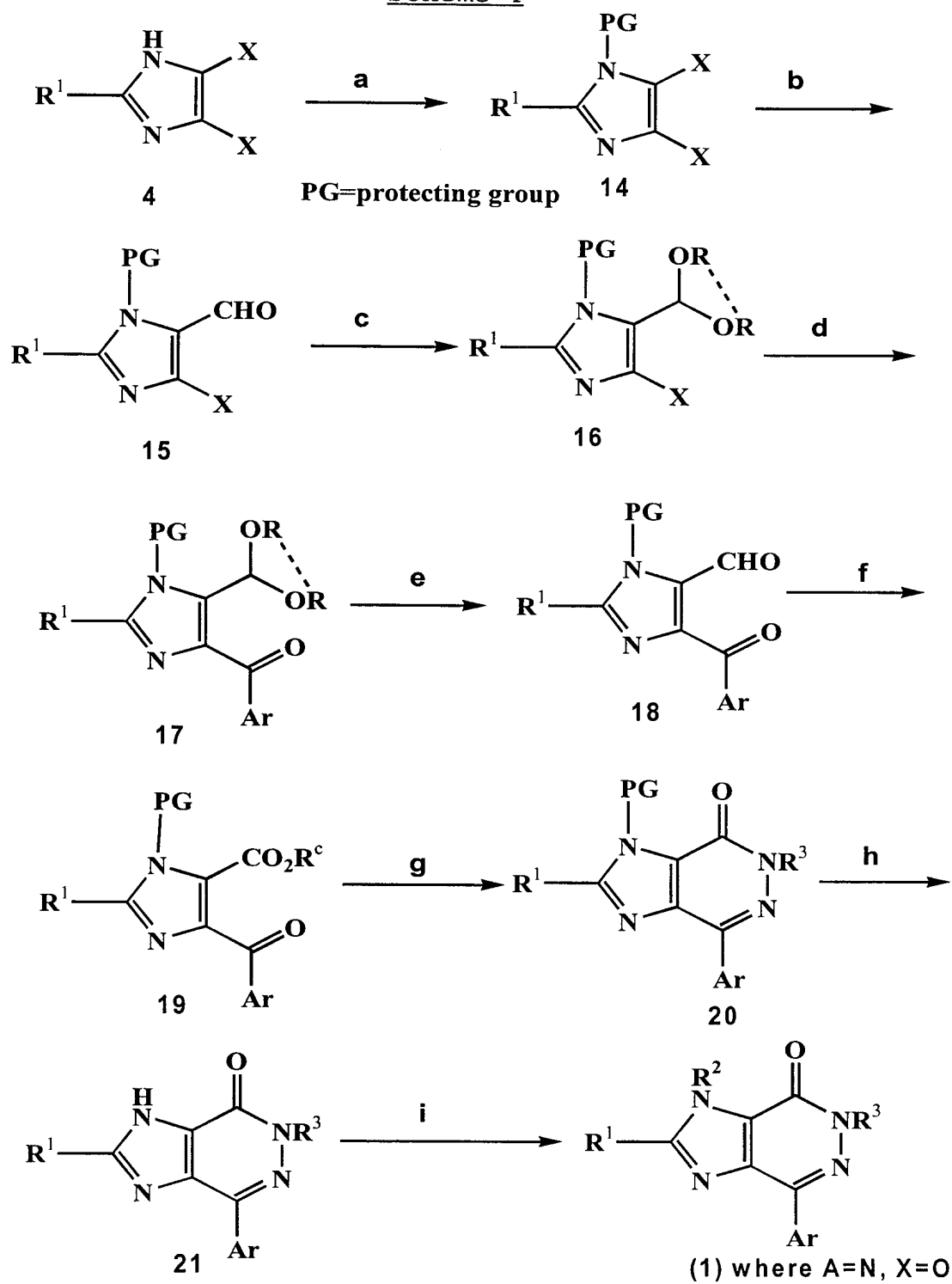
6 carbons, preferably acetonitrile), cyclic ethers  
(preferably tetrahydrofuran or 1,4-dioxane), N,N-  
dialkylformamides (preferably dimethylformamide), N,N-  
dialkylacetamides (preferably dimethylacetamide), cyclic  
5 amides (preferably N-methylpyrrolidin-2-one),  
dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic  
hydrocarbons (preferably benzene or toluene). Preferred  
temperatures range from ambient temperature to 150°C.

10

Scheme 3



Scheme 4



**Reagents:** (a) PG-X / base / solvent, (b) base, solvent, formylating agent, (c) acetal-forming reagent, (d) base, solvent, ArCOY, (e) acetal cleaving reagent, (f) 1. oxidizing agent, 2. ester-forming reagent or MCN, +/- acid, R<sup>c</sup>OH, (g) 1. NH<sub>2</sub>NH<sub>2</sub>, solvent, 2. R<sub>3</sub>X, base, solvent or R<sub>3</sub>NHNH<sub>2</sub>, solvent, (h) deprotecting agents, (i) Mitsunobu reaction or R<sub>2</sub>X, base, solvent

Alternatively, imidazo[4,5-d]pyridazin-7-ones may be obtained from intermediate (4) as shown in Scheme 4. The intermediate (4) may be converted to compound of formula (14) using protecting groups but not limited to benzyl, p-MeO-benzyl or benzyloxymethyl groups. Compound 14 may be converted to compound 20 using the conditions previously described for Scheme 1. Compound 10 may then be deprotected to its NH derivative (21) by standard conditions known in literature. Compound 21 may be alkylated under Mitsunobu conditions described in Scheme 1 or by alkylation using a base and alkyl halides in the presence of a solvent.

15

#### EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on a Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm ( $\delta$ ) from an internal tetramethylsilane standard in deuteriochloroform or deuteriodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH<sub>3</sub> as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

25  
30

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the

general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography (thin layer (TLC) or preparative) was performed on silica gel  
5 using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

The following examples are provided to describe the  
10 invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

15 Example 1 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

Part A: 4,5-dibromo-2-ethyl-1H-imidazole

Method A:

20 A solution of 2-ethylimidazole (57.6 g, 0.6 moles) in  $\text{CHCl}_3$  (700 mL) was cooled to 0- 5 °C and then bromine was added (76.8 mL, 1.5 moles) dropwise over 60 min under nitrogen atmosphere. The mixture was stirred at 5 °C for 60 mins and then at room temperature for 2  
25 days. TLC (1:10 MeOH /  $\text{CH}_2\text{Cl}_2$ ) revealed disappearance of starting material ( $R_f=0.25$ ) and showed a new spot ( $R_f=0.45$ ). The mixture was cooled back to 0 °C and a 2N aq. NaOH solution (750 mL) added dropwise to dissolve the yellow solid separated from the mixture.  
30 The aqueous layer was separated and extracted the organic layer with 250 mL of 2N NaOH. The combined aqueous extracts was acidified to pH 8.0 using a concentrated HCl solution. The cream-colored solid separated and it was filtered, washed with water and  
35 dried in vacuo at 50 °C to afford 55.0 g of desired

product (mp 149-150 °C, 36 % yield):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  
 $\delta$  1.27-1.3 (t, 3H,  $\text{CH}_3$ ), 2.7-2.8 (q, 2H,  $\text{CH}_2$ ). Mass  
spectrum ( $\text{CI-NH}_3$ )  $m/z$ : 255.0 ( $\text{M}+\text{H}$ ).

5 Method B :

To a solution of imidazole (2.32 g, 0.0242 moles) in  
DMF (30.0 mL) was added  $\text{KHCO}_3$  (6.1 g, 0.061 moles) and  
then added bromine (3.12 mL, 0.061 moles) dropwise  
over 30 mins. at room temp. The mixture was then  
10 stirred at 70 °C for 4 hours and then cooled to room  
temp. TLC (1:10 MeOH/  $\text{CH}_2\text{Cl}_2$ ) revealed a new spot  
( $R_f=0.45$ ) along with disappearance of starting  
material ( $R_f=0.25$ ). The inorganic materials were  
filtered, washed the inorganic solids with ethyl  
15 acetate and concentrated the filtrate in vacuo to an  
oil. The oil was treated with water (50.0 mL) and the  
resulting solid was filtered and dried to afford 4.59  
g of a solid ((mp, 149-150 °C, 75 % yield).

20 Part B: 4,5-dibromo-2-ethyl-1-(1-ethyl)propyl-1H-  
imidazole:

A mixture of part A material (8.3 g, 0.033 moles),  
triphenylphosphine (9.4 g, 0.036 moles) and molecular  
sieves (10 g) in THF (100 mL) was cooled to 0 to -5°C  
25 and then 3-pentanol (3.4 g, 0.039 moles) was added  
under nitrogen atmosphere. The mixture was stirred at  
0 °C for 30 mins and then diisopropylazodicarboxylate  
(7.2 g, 0.033 moles) was added dropwise over 20 min.  
The mixture was stirred at 0 °C for 2 hours followed  
30 by room temperature for 2 days and TLC (1:50 MeOH /  
 $\text{CH}_2\text{Cl}_2$ ) revealed a new spot at  $R_f=0.5$ . The reaction  
mixture was filtered, the collected solid was washed  
with dichloromethane and the solvent was removed in  
vacuo to afford yellow liquid. The crude was purified  
35 by flash column chromatography using chloroform as



eluent to afford 4.9 g (46.5 %) of colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.79-0.84 (t, 6H,  $2 \times \text{CH}_3$ ), 1.3-1.35 (t, 3H,  $\text{CH}_3$ ), 1.82-2.18 (m, 4H,  $2 \times \text{CH}_2$ ), 2.65-2.72 (q, 2H,  $\text{CH}_2$ ), 3.95 (m, 1H, CH). Mass spectrum (CI- $\text{NH}_3$ ):  $m/z$  325.0 (M+H).

Part C: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:

A solution of Part B material (3.7 g, 0.0114 moles) in THF (40.0 mL) was cooled to -78 °C under nitrogen atmosphere and then a 1.6 M n-BuLi solution in hexane (7.4 mL, 0.0119 moles) added dropwise over 30 mins. The mixture was stirred at -78 °C for 1h and then DMF (2.7 mL, 0.0342 moles) was added dropwise over 15 min. The mixture was stirred at -78 °C for 60 min and quenched with saturated  $\text{NH}_4\text{Cl}$  (10 mL) at -78 °C. TLC (1:50 MeOH /  $\text{CH}_2\text{Cl}_2$ ) revealed a new spot at  $R_f=0.55$  along with disappearance of starting material spot at  $R_f=0.5$ . The reaction mixture was extracted with diethyl ether (3 \* 25 mL), washed with brine and dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel using chloroform as eluent to afford 1.97 g (64 % yield) of colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.73-0.83 (t, 6H,  $2 \times \text{CH}_3$ ), 1.35-1.40 (t, 3H,  $\text{CH}_3$ ), 1.59-2.17 (m, 4H,  $2 \times \text{CH}_2$ ), 2.72-2.80 (q, 2H,  $\text{CH}_2$ ), 3.95 (m, 1H, CH), 9.67 (s, 1H, CHO). Mass spectrum (CI- $\text{NH}_3$ ):  $m/z$  275.1 (M+2H).

Part D: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde ethylene glycol acetal:

A mixture of part C material (1.75 g, 0.0064 moles) in benzene (150 mL) was treated with ethylene glycol (1.2 mL, 0.025 moles), pyridine (0.0035 moles) and p-toluenesulfonic acid mono hydrate (0.0035 moles). The

reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 24 hours and TLC (1:50 MeOH / CH<sub>2</sub>Cl<sub>2</sub>) revealed a new spot at R<sub>f</sub>=0.35 (visible under iodine). The reaction  
5 mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with 10 % sodium bicarbonate, brine and dried (MgSO<sub>4</sub>). The solvent was evaporated under reduced pressure to furnish yellow oil. The  
10 crude was purified by flash column chromatography on silica gel using 25 % ethyl acetate / chloroform mixture to afford 1.96 g (97 %) white solid (mp 70-71 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.78-0.89 (t, 6H, 2\*CH<sub>3</sub>), 1.29-1.36 (t, 3H, CH<sub>3</sub>), 1.77-1.90 (m, 4H, 2\*CH<sub>2</sub>), 2.70-2.73 (q, 2H, CH<sub>2</sub>), 3.98-4.3 (m, 5H, CH and 2\*CH<sub>2</sub>), 5.86 (s,  
15 1H, CH). Mass spectrum (CI-NH<sub>3</sub>): 317.1 (M<sup>+</sup>). Anal. calcd. for C<sub>13</sub>H<sub>22</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 49.22; H, 6.67; N, 8.83. Found: C, 49.43; H, 6.61; N, 8.78.

Part E: 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:  
20 A solution of part D material (1.08 g, 0.0034 moles) in THF (20.0 mL) was cooled to - 78 °C and then a 1.6 M n-BuLi in hexane (2.4 mL, 0.004 moles) was added dropwise over 15 min under nitrogen atmosphere. The  
25 mixture was stirred at -78 °C for 2.5 h and then a solution of 2,4-dichlorobenzoyl chloride (0.84 g, 0.004 moles) in THF (5.0 mL) was added over 15 mins. The mixture was stirred at -78 °C for 6 h followed by room temperature overnight and TLC (30:70 EtOAc /  
30 hexane) showed a new spot at R<sub>f</sub>= 0.43. The mixture was quenched with saturated NH<sub>4</sub>Cl (10.0 ml), extracted with ethyl acetate (3\*30 mL), washed with brine and dried (MgSO<sub>4</sub>). The solvent was stripped off in vacuo to afford crude product which was purified  
35 by flash column chromatography on a silica gel using

15 % EtOAc / hexane to afford 0.61 g (44 % yield) of desired product as yellow oil. Mass spectrum (CI-NH<sub>3</sub>): 411.2 (M<sup>+</sup>). The acetal was dissolved in acetone (15.0 mL) and treated with a 3.0 M aqueous HCl solution (30.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at R<sub>f</sub>=0.55. It was then quenched with saturated NaCl (50.0 mL), extracted with ethyl acetate (3\*50 mL), washed with brine and dried (MgSO<sub>4</sub>). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc / hexane to afford 0.28 g (51 % yield) of desired product as yellow solid (mp 85-86 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.785 (m, 6H, 2\*CH<sub>3</sub>), 1.28-1.33 (t, 3H, CH<sub>3</sub>), 1.90-2.23 (m, 4H, 2\*CH<sub>2</sub>), 2.74-2.82 (q, 2H, CH<sub>2</sub>), 3.98-4.05 (m, 1H, CH), 7.34-7.37 (d, 1H, aromatic), 7.45-7.46 (d, 1H, aromatic), 7.55-7.58 (d, 1H, aromatic). Mass spectrum (CI-NH<sub>3</sub>): 367 (M<sup>+</sup>). Anal. calcd. for C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 58.87; H, 5.50; N, 7.64. Found: C, 58.91; H, 5.60; N, 7.44.

Part F: Methyl 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-imidazo-5-carboxylate

A mixture of Part E material (0.367 g, 0.001 moles) in methanol (60 mL) was reacted with NaCN (Aldrich, 0.245 g, 0.005 moles, 5 equiv.), AcOH (Baker, 96 mg; 0.0016 moles, 1.6 equiv.) and MnO<sub>2</sub>, activated (Aldrich, 1.24 g, 0.021 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 18 h. TLC (1:50 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) revealed absence of starting material spot at R<sub>f</sub>=0.8 and showed a new spot at R<sub>f</sub>=0.44. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo and the crude was purified by

flash column chromatography on a silica gel using 1:100 MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 320 mg (mp 73-74 °C, 81 %) of white solid after crystallization from hexane. Anal. calcd. for C<sub>19</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>: C, 57.44; H, 5.58; N, 7.05. Found: C, 57.31; H, 5.45; N, 6.85.

Part G: Title Compound

A mixture of Part F material (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous hydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at R<sub>f</sub>=0.35. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel using 15:85 EtOAc / hexane initially and then methanol to afford 70 mg (74 % yield) of the product as white solid after tituration of the oil with diethyl ether (mp 246-247 °C). HRMS calcd. for C<sub>18</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>1</sub>: 379.1092. Found: 379.1070 (M+H).

Example 2 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)imidazo[4,5-d]pyridazin-7-one.

A mixture of Part F material of example 1 (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous methylhydrazine (0.150 g, 0.0033 moles) and refluxed under nitrogen for 8 days. TLC (1:50 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) showed a new spot at R<sub>f</sub>=0.55. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel 1:50 MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 30 mg (31 % yield) of the product as white solid (mp 94-95 °C). HRMS calcd. for C<sub>19</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>1</sub>: 393.1249. Found: 393.1250 (M+H).

Example 3 4-(2,4-dichlorophenyl)-2-ethyl-6-(N-ethyl)-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

To a solution of Part G of example 1 (0.1 g, 0.264 mmol) in benzene (5.0 mL) was added n-tetrabutylammonium bromide (8.5 mg, 0.0264 mmol), powdered KOH (15.0 mg, 0.264 mmol) and iodoethane (0.124 g, 0.79 mmol). The resultant mixture was stirred at room temperature under nitrogen for 20 h. TLC (1:50 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) showed a new spot at R<sub>f</sub>=0.73 along with disappearance of starting material (R<sub>f</sub>=0.33). The reaction mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), dried with MgSO<sub>4</sub> and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 58 mg (54 % yield) of the product as colorless oil. HRMS calcd. for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>Cl<sub>2</sub>O<sub>1</sub> : 407.1405. Found: 407.1404 (M+H).

Example 4 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-propyl)-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and 1-iodopropane and following the conditions outlined in example 3 to afford desired product as colorless oil (56mg, 51 % yield). Anal. calcd. for C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>Cl<sub>2</sub>O<sub>1</sub>: C, 59.86; H, 6.23; N, 13.30. Found: C, 59.86 ; H, 6.12 ; N, 13.13.

Example 5 6-(N-cyclopropylmethyl)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and bromomethylcyclopropane and following the conditions outlined in example 3 to

afford desired product as colorless oil (68 mg, 59 % yield). HRMS calcd. for  $C_{22}H_{27}N_4Cl_2O_1$ : 433.1562. Found: 433.1563 (M+H).

- 5 Example 6 4-Bis(2,4-trifluoromethylphenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one.

Part A: A solution of Part D material of example 1 in THF (30.0 mL) was cooled to -78 °C and then  
10 added dropwise 1.6 M n-BuLi in hexane over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,4-(CF<sub>3</sub>)<sub>2</sub>-Ph-COCl in 5.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred  
15 overnight. The reaction mixture was quenched with a saturated NH<sub>4</sub>Cl solution (50.0 ml), extracted with ethyl acetate (3\*30 mL), the combined organic extracts were washed with brine and the solvent was removed under vacuum to afford an orange yellow  
20 liquid (4.3 g). TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) along with a new spot at Rf=0.47. The crude was purified by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford 1.53 g (mp 105-  
25 106 °C, 64 % yield) of desired benzoyl derivative as white solid. Mass spec. (CI-NH<sub>3</sub>): 479.2 (M+H). Anal. calcd. for  $C_{22}H_{24}N_2O_3F_6$ : C, 55.23; H, 5.07; N, 5.87. Found; C, 54.96; H, 5.09; N, 5.72.

30 Part B: A solution of Part A material of example 6 (1.43 g, 2.9 mmoles) in acetone (30.0 mL) was cooled to 15 °C and then added 3M aq. HCl (60.0 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.63  
35 along with disappearance of starting material

(Rf=0.43). The solvent was removed under vacuum, extracted with ethyl acetate (3\*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.03 g (82 % yield) of desired aldehyde as yellow liquid. Mass spec. (NH<sub>3</sub>-CI): 435 (M+H). Anal. calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>F<sub>6</sub>: C, 55.30; H, 4.64; N, 6.46. Found; C, 55.03; H, 4.45; N, 6.27.

Part C: A mixture of Part B material of example 6 (0.434 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and MnO<sub>2</sub>, activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.63 and showed a new spot at Rf=0.55. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 350 mg (mp 57-58 °C, 75 %) of pale yellow solid. Mass spec. (NH<sub>3</sub>-CI): 465.3 (M+H). Anal. calcd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>F<sub>6</sub>: C, 54.31; H, 4.79; N, 6.03. Found: C, 53.92; H, 4.68; N, 5.80.

Part D: Title Compound:

A mixture of Part C material of example 6 (0.116 g, 0.250 mmoles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 3.3

mmoles, 13 equiv.) and refluxed under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed both starting material and product had identical R<sub>f</sub> values (0.55). The reaction mixture was cooled to room temperature and poured over 25 mL of water, extracted with EtOAc (3\*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford an oil which was crystallized from hexane to afford 16 mg (14 % yield; mp 139-140 °C) of white solid as desired product. HRMS calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>4</sub>O<sub>1</sub>F<sub>6</sub>: 461.1776. Found: 461.1763 (M+H).

**Example 7** (±)-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: To a solution of 4,5-dibromo-2-ethyl-1-(2-pentyl)-1H-imidazole (37.5 g, 0.116 moles, prepared according to the method described in Part B of example 1) in THF (250 mL) was cooled to -78 °C and then a 1.6 M n-BuLi in hexane added dropwise (76.0 mL, 0.122 moles) over 45 mins. The mixture was stirred at -78 °C for 1h (brown solution) and then added DMF (27.0 g, 0.348 moles) dropwise over 30 mins. The mixture was stirred at -78 °C for 60 mins. The reaction mixture was quenched with saturated ammonium chloride (100 mL) at -78 °C and brought to room temperature. The reaction mixture was extracted with ethyl ether (3\*100 mL), washed with brine and dried with anhydrous MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure to afford 31.6 g of crude yellow oil. The crude was purified by flash column chromatography on a silica gel using chloroform as eluent to afford 18.5 g (59 % yield) of



desired aldehyde as colorless oil. Anal. calcd. for  $C_{11}H_{17}N_2OBr$ ; C, 48.36; H, 6.27, N, 10.25. Found: C, 48.64; H, 6.01; N, 10.00.

- 5 Part B: A mixture of Part A material of example 7 (18.5 g, 0.068 moles) in benzene (250 mL) was treated with ethylene glycol (16.4 g, 0.264 moles), pyridine (2.7 g, 0.034 moles) and p-toluenesulfonic acid monohydrate (6.5 g, 0.034 moles). The reaction
- 10 mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 36h. TLC (30:70 EtOAc/hexane) revealed a new spot at  $R_f=0.42$  (visible under iodine) along with disappearance of starting material ( $R_f=0.54$ ). The reaction mixture was
- 15 cooled to room temperature, diluted with EtOAc (250 mL), washed with 10 % sodium bicarbonate (2\*250 mL), brine and dried ( $MgSO_4$ ). The solvent was evaporated under reduced pressure to furnish acetal as white solid (20.7 g, mp 69-70 °C, 96 %). Mass spectrum (CI-
- 20  $NH_3$ ): 317.1 ( $M^+$ ). Anal. calcd. for  $C_{13}H_{22}N_2O_2Br_1$ ; C, 49.22; H, 6.67, N, 8.83. Found: C, 49.38; H, 6.62; N, 8.68.

- Part C: A solution of Part B material of example 7
- 25 (2.73 g, 0.01moles) in THF (30 mL) was cooled to -78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL) over 15 mins. The mixture was stirred at -78°C for 2 1/2 h and then added a solution of 2,4-dichlorobenzoyl chloride in 5.0 mL of THF over 15
- 30 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd.  $NH_4Cl$  (50.0 ml), extracted with ethyl acetate (3\*30 mL), washed with brine and stripped off the solvent in vacuum to
- 35 afford orange yellow liquid (4.3 g). TLC (30:70

- EtOAc/hexane) of the crude showed absence of starting material spot ( $R_f=0.4$ ) and a new spot at  $R_f=0.47$ . The crude was purified by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford 2.4 g (mp 129-130 °C, 59 % yield) of benzoyl derivative as white solid. Mass spec. (CI-NH<sub>3</sub>): 411 (M<sup>+</sup>). Anal. calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>Cl<sub>2</sub>: C, 58.40; H, 5.88; N, 6.81. Found: C, 58.45; H, 5.95; N, 6.68.
- 10 Part D: A solution of Part C material of example 7 (2.3 g, 0.056 moles) in acetone (60 mL) was cooled to 15 °C and then added 3M aq. HCl (120 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at  $R_f=0.58$  along with disappearance of starting material ( $R_f=0.43$ ). The solvent was removed under vacuum, extracted with ethyl acetate (3\*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid (2.4 g). The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.46 g (71 % yield) of keto aldehyde derivative as yellow solid (mp 43-44 °C). Mass spec. (NH<sub>3</sub>-CI): 367 (M<sup>+</sup>). Anal. calcd. for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>: C, 58.87; H, 5.50; N, 7.64. Found: C, 58.96; H, 5.34; N, 7.46.

- Part E : A mixture of Part D material of example 7 (1.0 g, 0.0027 moles) in methanol (50 mL) was treated with NaCN (Aldrich, 0.67 g, 0.0136 moles, 5 equiv.), AcOH (Baker, 260 mg; 0.00432 moles, 1.6 equiv.) and MnO<sub>2</sub>, activated (Aldrich, 3.34 g, 0.057 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at  $R_f=0.58$  and showed a new spot at  $R_f=0.4$ . The

reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford 0.98 g of yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 910 mg (85 %) of keto ester derivative as yellow oil. Mass spec.: 397.2 ( $M^+$ ). Anal. calcd. for  $C_{19}H_{22}N_2O_3Cl_2$ : C, 57.44; H, 5.58; N, 7.05. Found: C, 57.25; H, 5.70; N, 6.80.

Part F: Title Compound: A mixture of Part E material of example 7 (0.100 g, 0.00025 moles) in ethylene glycol (2 mL) was treated with anhydrous methylhydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 4 h. TLC (30:70 EtOAc/hexane) revealed a new spot ( $R_f=0.44$ ) along with disappearance of starting material ( $R_f=0.4$ ). The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3\*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 42 mg of white solid (43 %, mp 89-90 °C). Mass spec. (CI-NH<sub>3</sub>): 393.2 ( $M^+$ ). Anal. calcd. for  $C_{19}H_{22}N_4Cl_2O$ : C, 58.02; H, 5.65; N, 14.24. Found: C, 58.32; H, 5.59; N, 14.14.

Example 8 (+)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

A mixture of Part E material of example 7 (0.460 g, 0.00115 moles) in ethylene glycol (5 mL) was treated with anhydrous hydrazine (0.48 g, 0.0151 moles) and refluxed under nitrogen for 4 h. TLC

(30:70 EtOAc/hexane) revealed a new spot ( $R_f=0.44$ ) along with disappearance of starting material ( $R_f=0.4$ ). The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3\*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 310 mg of white solid (71 %, mp 217-18 °C). Mass spec. (CI-NH<sub>3</sub>): 379.2 (M<sup>+</sup>). Anal. calcd. for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>Cl<sub>2</sub>O: C, 57.00; H, 5.33; N, 14.77. Found: C, 57.02; H, 5.35; N, 14.59.

**Example 9** (+)-4-(2,5-dimethyl-4-methoxyphenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: Synthesis of 2,5-dimethyl-4-methoxybenzoyl chloride: To a stirred mixture of 2,5-dimethyl-4-methoxybenzaldehyde (6.7 g, 0.004 moles) in acetone (140 mL) at 60 °C was added KMnO<sub>4</sub> (8.46 g, 0.0054 moles) dissolved in water (250 mL) dropwise over 30 mins. The reaction mixture quickly turned into brown suspended solution. The reaction mixture was further continued for 1h. The reaction mixture was cooled to room temp., filtered through celite and extracted with diethyl ether. The aq. layer was acidified with con. HCl, filtered the white solid separated, washed with water and dried at 50 °C for 30 mins under vacuum to afford 3.46 g of carboxylic acid as white solid (mp 161-162 °C, 48 % yield). The carboxylic acid (3.4 g, 0.0189 moles) was dissolved in 75 mL of anhydrous benzene and added few drops of pyridine followed by addition of thionyl chloride (5.0 mL, 0.0689, 3.65 equiv., fw 118.97, d 1.631).

The resultant mixture was refluxed at reflux for 20 h. The solvent was removed under vacuum, the solid thus resulted was treated with 5.0 mL of hexane and filtered the undissolved white solid (3.7 g, mp 84-85 °C, 98.7 %).

Part B: A solution of Part B material of example 7 (2.73 g, 0.01 moles) in THF was cooled to -78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL, 0.0115 moles) over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,5-(Me)<sub>2</sub>-4-OMe-Ph-COCl (2.2 g, 0.012 moles) in 10.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd. NH<sub>4</sub>Cl (50.0 ml), extracted with ethyl acetate (3\*30 mL), washed with brine and stripped off the solvent in vacuum to afford orange yellow liquid. TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (R<sub>f</sub>=0.4) along with product spot appeared at R<sub>f</sub>=0.38. The crude was purified by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford 1.53 g (mp 160-162 °C, 38 % yield) of desired benzoyl derivative as pale yellow solid. Mass spec. (CI-NH<sub>3</sub>): 401.3 (M+H). Anal. calcd. for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.97; H, 8.05; N, 6.99. Found; C, 69.05; H, 8.10; N, 6.33.

Part C: A solution of Part B material of example 9 (1.4 g, 0.0035 moles) in acetone (30 mL) was cooled to 15 °C and then added 3M aq. HCl (60 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed product spot at 0.56. The solvent was removed under vacuum, extracted with ethyl acetate (3\*50 mL), washed with brine and

stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane, followed by 1% MeOH/dichloromethane as eluents to afford 0.48 g (39 % yield) of desired product as yellow liquid. HRMS calcd. for  $C_{21}H_{29}N_2O_3$ : 357.2178. Found: 357.2169 (M+H).

Part D: A mixture of Part C material of example 9 (0.357 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 Mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and  $MnO_2$ , activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at  $R_f=0.56$  and showed a new spot at  $R_f=0.30$ . The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 205 mg (53 %) of ketoester derivative as pale yellow oil. HRMS calcd. for  $C_{22}H_{30}N_2O_4$ : 386.2205. Found: 387.2264 (M+H).

Part E: A mixture of Part D material of example 9 (0.100 g, 0.000259 moles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 0.0033 moles, 13 equiv.) and refluxed under nitrogen for 14 h. TLC (30:70 EtOAc/hexane) revealed a new spot ( $R_f=0.40$ ) along with disappearance of starting material ( $R_f=0.3$ ). The reaction mixture was cooled to room temp and poured over 25 mL of water,

extracted with EtOAc (3\*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford 43 mg  
5 (43 % yield) of a solid: HRMS calcd. for  $C_{22}H_{31}N_4O_2$ : 383.2447. Found: 383.2433 (M+H).

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

10

The examples delineated in Tables 1, 2, 3 and 4 may be prepared by the methods outlined in Examples 1, 2 or 3 or combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is  
15 butyl, Ex is Example, amorph. is amorphous.

## EXAMPLE 544

4-(2,4-Dichlorophenyl)-2-ethyl-6-(N-methyl)-  
imidazo[4,5-d]pyridazin-7-one

5

Part A: Synthesis of 1-[(Benzyloxy)methyl]4,5-dibromo-2-ethylimidazole: To a mechanically stirred solution of 4,5-dibromo-2-ethylimidazole (25.4 g, 0.1 mole,) in anhydrous DMF (250 mL) was treated with  
10  $K_2CO_3$  (69.1 g, fw=138.2, 0.5 moles, 5 equiv.) followed by dropwise addition of benzyl chloromethyl ether (18.5 g, 0.11 moles, 93 % pure, TCI, fw=156.61) and stirred overnight at room temp under nitrogen for 20 h. TLC (30:70 EtOAc / hexane) revealed absence of  
15 starting material imidazole ( $R_f=0.2$ ) along with formation of product ( $R_f=0.71$ ). The reaction mixture was filtered, washed the solid with dichloromethane and the combined filtrate was evaporated under reduced pressure and purified the crude (47 g) by  
20 flash column chromatography (dichloromethane eluent) to afford 31.75 g (85 %) of colorless oil. Mass spectrum ( $m/z=375$ ,  $M+H$ ).

Part B: Synthesis of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formylimidazole: A solution of 1-[(Benzyloxy)methyl]-4,5-dibromo-2-ethylimidazole (28.0 g, 75.0 mmol, Part A of example 544) in THF (300 mL) was cooled to -78 °C under nitrogen atmosphere and then added dropwise 1.6 M n-BuLi in  
30 hexane (51.75 mL, 82.5 mmol, Aldrich) over 30 mins. The mixture was stirred at -78 °C for 30 mins and then added DMF (16.5 g, 225 mmol, Aldrich) dropwise over 15 mins. The mixture was stirred at -78 °C for 30 mins. A small portion of the reaction mixture was  
35 quenched with satd.  $NH_4Cl$  at -78 °C. TLC (30:70 EtOAc/hexane) revealed both starting material and product showed almost identical  $R_f$  values (0.71 & 0.70) along with another minor spot at  $R_f=0.15$ . However, mass spectrum (CI- $NH_3$ ) revealed absence of  
40 starting material and formation of product ( $m/z=325$ ,  $M+2H$ ). The reaction mixture was quenched with satd. ammonium chloride (20 mL) at -78 °C and brought to room temp. The reaction mixture was extracted with ethyl acetate (3 x 100 mL), washed with brine and  
45 dried with anhydrous  $MgSO_4$ . The solvent was evaporated under reduced pressure to afford crude yellow oil. The crude was purified by flash column chromatography on a silica gel using dichloromethane



as eluent to afford 22.6 g (93 %) of colorless oil.  
HRMS calcd. for  $C_{14}H_{16}N_2O_2Br$ : 323.0395. Found: 323.0394  
(M+H).

5 Part C: 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-  
formylimidazole ethylene acetal: A mixture of 1-  
[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-  
imidazole (22.6 g, 0.0699 moles) in benzene (400 mL)  
was treated with ethylene glycol (16.9 g, 0.273  
10 moles, fw 62, 3.9 equiv.), pyridine (2.76 g, 0.03495  
moles, fw=79.1, 0.5 equiv.) and p-toluenesulfonic  
acid monohydrate (6.6 g, 0.03495 moles, fw=190, 0.5  
equiv). The reaction mixture was heated at reflux in  
a 20 mL capacity Dean-Stark trap equipped apparatus  
15 for 24 hours. TLC (30:70 EtOAc / hexane) revealed a  
new spot at  $R_f=0.35$  (visible under iodine) along with  
disappearance of starting material ( $R_f=0.70$ ). The  
reaction mixture was cooled to room temperature,  
diluted with EtOAc (100 mL), washed with 10 % sodium  
20 bicarbonate, brine and dried ( $MgSO_4$ ). The solvent was  
evaporated under reduced pressure to furnish yellow  
oil. The crude was purified by flash column  
chromatography on silica gel using 25 % ethyl acetate  
/ hexane mixture to afford 22.8 g (89 %) colorless  
25 oil.  $^1H$  NMR ( $CDCl_3$ ): 1.29-1.33 (t, 3H,  $CH_3$ ), 2.71-2.78  
(q, 2H,  $CH_2$ ), 3.96 (s, 4H, 2 x  $OCH_2$ ), 4.55 (s, 2H,  
 $CH_2$ ), 5.4 (s, 2H,  $CH_2$ ), 5.88 (s, 1H, CH), 7.27-7.38  
(M, 5H, aromatic). HRMS calcd. for  $C_{16}H_{20}N_2O_3Br_1$ :  
367.0658. Found: 367.0653 (M+H).

30 Part D: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-  
2-ethyl-5-formylimidazole ethylene acetal: A solution  
of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-  
imidazole ethylene acetal (22.5 g, 0.0613 moles,  
35 fw=367.25, Part C of Example 544) in THF (200.0 mL)  
was cooled to -78 °C and then added dropwise 1.6 M n-  
BuLi in hexane (43.7 mL, 0.071 moles, 1.1 equiv.) over  
15 mins under nitrogen atmosphere. The mixture was  
stirred at -78°C for 90 mins and then added a solution  
40 of 2,4-dichlorobenzoyl chloride (14.3 g, 0.071 moles,  
1.1 equiv.) in THF (5.0 mL) over 15 mins. The mixture  
was stirred at -78°C for 4 h followed by room  
temperature overnight. TLC (30:70 EtOAc / hexane)  
showed a new spot at  $R_f=0.38$  along with disappearance  
45 of starting material ( $R_f=0.35$ ). The mixture was  
quenched with saturated  $NH_4Cl$  (100.0 ml), extracted  
with ethyl acetate (3 x 150 mL), washed with brine and  
dried ( $MgSO_4$ ). The solvent was stripped off in vacuo

- to afford crude product (yellow oil) which was purified by flash column chromatography on a silica gel using 20 % EtOAc / hexane to afford 12.3 g (mp 95-96 °C , 43 % yield) of desired product as white solid.
- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.22-1.27 (t, 3H, CH<sub>3</sub>), 2.74-2.81 (q, 2H, CH<sub>2</sub>), 3.94-4.03 (m, 4H, 2 x OCH<sub>2</sub>), 4.59 (s, 2H, CH<sub>2</sub>), 5.54 (s, 2H, CH<sub>2</sub>), 6.62 (s, 1H, CH), 7.27-7.54 (m, 8H, aromatic). Mass spectrum (CI-NH<sub>3</sub>): 461 (M<sup>+</sup>). Anal. calcd. for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>: C, 59.88; H, 4.82; N, 6.07. Found: C, 59.77; H, 4.78; N, 5.93.
- 10

- Part E: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-formylimidazole : The above acetal (12.1 g, 0.0263 moles, Part D of Example 544) was dissolved in acetone (200.0 mL) and treated with 3.0 M aqueous HCl (400.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at R<sub>f</sub>=0.55. It was then quenched with saturated NaCl (50.0 mL), extracted with ethyl acetate (3 x 150 mL), washed with brine and dried (MgSO<sub>4</sub>). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc / hexane to afford 6.0 g (55 % yield) of desired product as colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.27-1.32 (t, 3H, CH<sub>3</sub>), 2.78-2.86 (q, 2H, CH<sub>2</sub>), 4.62 (s, 2H, CH<sub>2</sub>), 5.92 (s, 2H, CH<sub>2</sub>), 7.25-7.55 (m, 8H, aromatic), 10.39 (s, 1H, CHO). Mass spectrum (CI-NH<sub>3</sub>): 417 (M<sup>+</sup>). Anal. calcd. for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Cl<sub>2</sub>: C, 60.44; H, 4.36; N, 6.71. Found: C, 60.43; H, 4.45; N, 6.49.
- 15
- 20
- 25
- 30

- Part F: Methyl 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-imidazole carboxylate: A mixture of 2-Et-5-CHO-imidazole derivative (6.0 g, fw=417, 14.34 mmoles, Part E of Example 544) in methanol (120 mL) was treated with NaCN (Aldrich, fw=49, 3.54 g, 12.0 mmoles, 5 equiv.), AcOH (Baker, fw = 60, 1.38 g; 22.92 mmoles, 1.6 equiv.) and MnO<sub>2</sub>, activated (Aldrich, fw=86.94, 25.8 g, 301.2 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 3 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material at R<sub>f</sub>=0.55 and showed a new spot at R<sub>f</sub>=0.35. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to
- 35
- 40
- 45

afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc / hexane as eluent to afford 4.62 g (72 % yield) of colorless oil. HRMS calcd. for  $C_{22}H_{21}Cl_2N_2O_4$ : 447.0878. Found: 447.0870 (M+H). Anal. calcd. for  $C_{22}H_{20}Cl_2N_2O_4$ : C, 59.07; H, 4.52; N, 6.26. Found: C, 58.97; H, 4.65; N, 6.07

10 Part G: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-imidazo[4,5-d]pyridazin-7-one: A mixture of imidazole deriv. (3.55 g, fw=447, 0.00794 moles, Part F of Example 544) in ethanol (50 mL) was treated with anhydrous hydrazine (3.3 g, 0.102 moles, 13 equiv) and refluxed under nitrogen for 2 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material (Rf=0.35) and showed a new spot (Rf=0.27). The solvent was removed under vacuo and purified the crude titrating with 1:1 EtOH / hexane to afford 2.2 g (65 % yield, mp 174-175 °C) of desired product as white solid. Mass spectrum (APCI): (m/z=429, M<sup>+</sup>). Anal. calcd. for  $C_{21}H_{18}N_4Cl_2O_2$ : C, 58.75; H, 4.24; N, 13.05. Found: C, 58.65; H, 4.30; N, 12.86.

25 Part H: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one: To a solution of the above 6H-imidazo[4,5-d]pyridazin-7-one derivative (2.2 g, 0.005 moles, Part G of Example 544) in benzene (100 mL) was added powdered KOH (0.43 g, 0.0076 moles), n-Bu<sub>4</sub>NBr (161 mg, 0.0005 moles) and MeI (excess) at room temperature. The reaction mixture appeared white suspension and stirred for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.40 along with disappearance of starting material (Rf=0.27). The reaction mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), dried with MgSO<sub>4</sub> and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc / hexane as eluent to afford 1.96 g (86 % yield, mp 80-81 °C) of the product as white solid. Anal. calcd. for  $C_{21}H_{20}N_4Cl_2O_2$ : C, 59.60; H, 4.56; N, 12.64. Found: C, 59.61; H, 4.57; N, 12.52.

45 Part I: Title Compound: A mixture of 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one (2.6 g, fw=443.33, 5.87 mmol, Part H of Example 544) in ethanol (100 mL) was treated with conc. HCl (2.93 mL,

29.3 mmol, 5.0 equiv) and refluxed under nitrogen for 60 mins. TLC (30:70 EtOAc/hexane) revealed disappearance of starting material ( $R_f=0.40$ ) and a new spot appeared near the origin. The reaction mixture was cooled to room temperature adjusted the pH using  $\text{NaHCO}_3$  and the solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 50 % EtOAc / hexane to afford 1.85 g (mp 234-235 °C, 97 % yield) of desired product as white solid. NMR ( $\text{CDCl}_3$ ): 1.46-1.52 (t, 3H,  $\text{CH}_3$ ), 3.04-3.11 (q, 2H,  $\text{CH}_2$ ), 4.04 (s, 3H, N-Me), 7.38-7.41 (d, 2H, aromatic), 7.54-7.57 (m, 3H, aromatic), 13.65 (bs, 1H, NH). Mass spectrum ( $\text{CI-NH}_3$ ):  $m/z=323$  ( $M^+$ ). HRMS calcd. for  $\text{C}_{14}\text{H}_{13}\text{N}_4\text{Cl}_2\text{O}_1$ : 323.0466. Found: 323.0477 ( $M+H$ ). Anal. calcd. for  $\text{C}_{14}\text{H}_{12}\text{N}_4\text{Cl}_2\text{O}_1$ : C, 52.03; H, 3.74. Found: C, 51.92 ; H, 4.07.

## EXAMPLE 546

1-Butyl-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

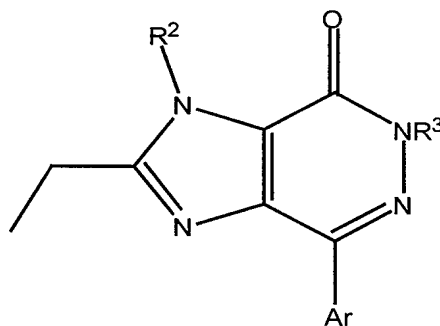
To a solution of imidazopyridazin-7-one deriv. (32.3 mg, fw=323, 0.1 mmol, Part I of example 544) in DMF (2.0 mL) under nitrogen atmosphere was added 60 % NaH in oil dispersion (6.0 mg, fw=24, 0.15 mmol, 1.5 equiv.). The mixture was stirred at room temp for 5 mins and then added 1-bromobutane (27.6 mg, fw=184, 0.15 mmol, 1.5 equiv) to reaction mixture and stirred overnight. TLC (30:70 EtOAc/hexane) showed a new spot at  $R_f=0.36$  along with disappearance of starting material ( $R_f=\text{origin}$ ). The reaction mixture was diluted with water (5.0 mL), extracted with EtOAc (3\*5 mL), washed with brine (10 mL), dried with  $\text{MgSO}_4$  and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc/hexane as eluent to afford 29.7 mg (78 % yield) of the product as colorless oil. HRMS calcd. for  $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_1\text{Cl}_2$ : 379.1092. Found: 379.1086 ( $M+H$ ).

## EXAMPLE 548

4-(2,4-dichlorophenyl)-2-ethyl-1-[1-(ethyl)pentyl]-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

To a solution of imidazopyridazin-7-one deriv. (48.3 mg, fw=323, 0.15 mmol, Part I of Example 544) in THF (2.0 mL) under nitrogen atmosphere was added PPh<sub>3</sub> (43.3 mg, fw=262.29, 0.165 mmol, 1.1 equiv.), and 3-heptanol (21.0 mg, Aldrich, 0.18 mmol, fw=116.2, 1.2 equiv.). The mixture was cooled to -20 °C and then added diisopropylazodicarboxylate (33.3 microlit., Aldrich, 0.165 mmol, fw=202, 1.1 equiv.) dropwise using a syringe. The resultant mixture was stirred at -20 °C for 2 h followed by room temperature for 20h. TLC (30:70 EtOAc/hexane) showed a new spot at R<sub>f</sub>=0.53 along with trace amount of starting material (R<sub>f</sub>=origin). The reaction mixture was concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 15:85 EtOAc/hexane as eluent to afford 37 mg (58 % yield, 110-111 °C) of the product as white solid. HRMS calcd. for C<sub>21</sub>H<sub>27</sub>N<sub>4</sub>O<sub>1</sub>Cl<sub>2</sub>: 421.1562. Found:421.1555 (M+H).

Table 1



25

	<u>Ex.</u>	<u>R<sub>3</sub></u>	<u>R<sub>2</sub></u>	<u>Ar</u>	<u>mp (°C)</u>
30	2	Me	3-pentyl	2,4-Cl <sub>2</sub> -Ph	94-95
	3	Et	3-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	4	Pr	3-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	5	CH <sub>2</sub> -c-C <sub>3</sub> H <sub>5</sub>	3-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	6	Me	3-pentyl	2,4-(CF <sub>3</sub> ) <sub>2</sub> -Ph	139-140
35	7	Me	2-pentyl	2,4-Cl <sub>2</sub> -Ph	89-90
	9	Me	2-pentyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph	amorph.

	10	Me	CH (Et) CH <sub>2</sub> OH	2,4-Cl <sub>2</sub> -Ph	
	12	Me	CH (Et) CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
	13	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
	14	Me	2-butyl	2,4-Cl <sub>2</sub> -Ph	
5	15	Me	cyclobutyl	2,4-Cl <sub>2</sub> -Ph	oil
	16	Me	cyclopentyl	2,4-Cl <sub>2</sub> -Ph	180-181
	17	Me	CH (Me) cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	18	Me	CH (Me) cyclopropyl	2,4-Cl <sub>2</sub> -Ph	oil
	19	Me	CH (Et) cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
10	20	Me	CH (Et) cyclopropyl	2,4-Cl <sub>2</sub> -Ph	117-118
	21	Me	CH (Me) CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	22	Me	CH (OH) CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	23	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	24	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
15	25	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	26	Me	CH (CH <sub>2</sub> OMe) cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	27	Me	CH (CH <sub>2</sub> OMe) cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	28	Me	CH (CH <sub>2</sub> OEt) cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	29	Me	CH (CH <sub>2</sub> OEt) cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
20	30	Me	CH (cyclobutyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	
	31	Me	CH (cyclopropyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	140-142
	32	Me	CH (Et) CH <sub>2</sub> CONMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	
	33	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	
	34	Me	CH (CH <sub>2</sub> OMe) Me	2,4-Cl <sub>2</sub> -Ph	
25	35	Me	CH (CH <sub>2</sub> OMe) Et	2,4-Cl <sub>2</sub> -Ph	
	36	Me	CH (CH <sub>2</sub> OMe) Pr	2,4-Cl <sub>2</sub> -Ph	
	37	Me	CH (CH <sub>2</sub> OEt) Me	2,4-Cl <sub>2</sub> -Ph	
	38	Me	CH (CH <sub>2</sub> OEt) Et	2,4-Cl <sub>2</sub> -Ph	
	39	Me	CH (CH <sub>2</sub> OEt) Pr	2,4-Cl <sub>2</sub> -Ph	
30	40	Me	CH (CH <sub>2</sub> C≡CMe) Et	2,4-Cl <sub>2</sub> -Ph	
	41	Me	CH (CH <sub>2</sub> CH=CHMe) Et	2,4-Cl <sub>2</sub> -Ph	
	42	Me	CH (Et) CH <sub>2</sub> OH	2,4,6-Me <sub>3</sub> -Ph	
	43	Me	CH (Et) CH <sub>2</sub> OMe	2,4,6-Me <sub>3</sub> -Ph	
	44	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2,4,6-Me <sub>3</sub> -Ph	
35	45	Me	3-pentyl	2,4,6-Me <sub>3</sub> -Ph	

	46	Me	2-pentyl	2,4,6-Me <sub>3</sub> -Ph
	47	Me	2-butyl	2,4,6-Me <sub>3</sub> -Ph
	48	Me	cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	49	Me	cyclopentyl	2,4,6-Me <sub>3</sub> -Ph
5	50	Me	CH(Me) cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	51	Me	CH(Me) cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	52	Me	CH(OMe) cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	53	Me	CH(Et) cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	54	Me	CH(Et) cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
10	55	Me	CH(Me) CH <sub>2</sub> -cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	56	Me	CH(Me) CH <sub>2</sub> -cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	57	Me	CH(OMe) CH <sub>2</sub> -cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	58	Me	CH(Et) CH <sub>2</sub> -cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	59	Me	CH(Et) CH <sub>2</sub> -cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
15	60	Me	CH(CH <sub>2</sub> OMe) cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	61	Me	CH(CH <sub>2</sub> OMe) cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	62	Me	CH(CH <sub>2</sub> OEt) cyclobutyl	2,4,6-Me <sub>3</sub> -Ph
	63	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	2,4,6-Me <sub>3</sub> -Ph
	64	Me	CH(cyclobutyl) <sub>2</sub>	2,4,6-Me <sub>3</sub> -Ph
20	65	Me	CH(cyclopropyl) <sub>2</sub>	2,4,6-Me <sub>3</sub> -Ph
	66	Me	CH(Et) CH <sub>2</sub> CONMe <sub>2</sub>	2,4,6-Me <sub>3</sub> -Ph
	67	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4,6-Me <sub>3</sub> -Ph
	68	Me	CH(CH <sub>2</sub> OMe) Me	2,4,6-Me <sub>3</sub> -Ph
	69	Me	CH(CH <sub>2</sub> OMe) Et	2,4,6-Me <sub>3</sub> -Ph
25	70	Me	CH(CH <sub>2</sub> OMe) Pr	2,4,6-Me <sub>3</sub> -Ph
	71	Me	CH(CH <sub>2</sub> OEt) Me	2,4,6-Me <sub>3</sub> -Ph
	72	Me	CH(CH <sub>2</sub> OEt) Et	2,4,6-Me <sub>3</sub> -Ph
	73	Me	CH(CH <sub>2</sub> OEt) Pr	2,4,6-Me <sub>3</sub> -Ph
	74	Me	CH(CH <sub>2</sub> C≡CMe) Et	2,4,6-Me <sub>3</sub> -Ph
30	75	Me	CH(CH <sub>2</sub> CH=CHMe) Et	2,4,6-Me <sub>3</sub> -Ph
	76	Me	CH(Et) CH <sub>2</sub> OH	2,4-Me <sub>2</sub> -Ph
	77	Me	CH(Et) CH <sub>2</sub> OMe	2,4-Me <sub>2</sub> -Ph
	78	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Me <sub>2</sub> -Ph
	79	Me	3-pentyl	2,4-Me <sub>2</sub> -Ph
35	80	Me	2-pentyl	2,4-Me <sub>2</sub> -Ph

	81	Me	2-butyl	2,4-Me <sub>2</sub> -Ph	
	82	Me	cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	83	Me	cyclopentyl	2,4-Me <sub>2</sub> -Ph	
	84	Me	CH(Me) cyclobutyl	2,4-Me <sub>2</sub> -Ph	
5	85	Me	CH(OH) cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	86	Me	CH(Me) cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	87	Me	CH(OH) cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	88	Me	CH(Et) cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	89	Me	CH(Et) cyclopropyl	2,4-Me <sub>2</sub> -Ph	
10	90	Me	CH(Me) CH <sub>2</sub> -cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	91	Me	CH(Me) CH <sub>2</sub> -cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	92	Me	CH(OMe) CH <sub>2</sub> -cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	93	Me	CH(Et) CH <sub>2</sub> -cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	94	Me	CH(Et) CH <sub>2</sub> -cyclopropyl	2,4-Me <sub>2</sub> -Ph	
15	95	Me	CH(CH <sub>2</sub> OMe) cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	96	Me	CH(CH <sub>2</sub> OMe) cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	97	Me	CH(CH <sub>2</sub> OEt) cyclobutyl	2,4-Me <sub>2</sub> -Ph	
	98	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	2,4-Me <sub>2</sub> -Ph	
	99	Me	CH(cyclobutyl) <sub>2</sub>	2,4-Me <sub>2</sub> -Ph	
20	100	Me	CH(cyclopropyl) <sub>2</sub>	2,4-Me <sub>2</sub> -Ph	
	101	Me	CH(Et) CH <sub>2</sub> CONMe <sub>2</sub>	2,4-Me <sub>2</sub> -Ph	
	102	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4-Me <sub>2</sub> -Ph	
	103	Me	CH(CH <sub>2</sub> OMe) Me	2,4-Me <sub>2</sub> -Ph	
	104	Me	CH(CH <sub>2</sub> OMe) Et	2,4-Me <sub>2</sub> -Ph	
25	105	Me	CH(CH <sub>2</sub> OMe) Pr	2,4-Me <sub>2</sub> -Ph	
	106	Me	CH(CH <sub>2</sub> OEt) Me	2,4-Me <sub>2</sub> -Ph	
	107	Me	CH(CH <sub>2</sub> OEt) Et	2,4-Me <sub>2</sub> -Ph	
	108	Me	CH(CH <sub>2</sub> OEt) Pr	2,4-Me <sub>2</sub> -Ph	
	109	Me	CH(CH <sub>2</sub> C≡CMe) Et	2,4-Me <sub>2</sub> -Ph	
30	110	Me	CH(CH <sub>2</sub> C≡CMe) Et	2,4-Me <sub>2</sub> -Ph	
	111	Me	CH(Et) CH <sub>2</sub> OH	2-Me-4-MeO-Ph	
	112	Me	CH(Et) CH <sub>2</sub> OMe	2-Me-4-MeO-Ph	
	113	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2-Me-4-MeO-Ph	
	114	Me	3-pentyl	2-Me-4-MeO-Ph	125-126
35	115	Me	2-pentyl	2-Me-4-MeO-Ph	oil



	116	Me	2-butyl	2-Me-4-MeO-Ph	
	117	Me	cyclobutyl	2-Me-4-MeO-Ph	
	118	Me	cyclopentyl	2-Me-4-MeO-Ph	
	119	Me	CH(Me) cyclobutyl	2-Me-4-MeO-Ph	
5	120	Me	CH(Me) cyclopropyl	2-Me-4-MeO-Ph	
	121	Me	CH(Et) cyclobutyl	2-Me-4-MeO-Ph	
	122	Me	CH(Et) cyclopropyl	2-Me-4-MeO-Ph	
	123	Me	CH(Me) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-Ph	
	124	Me	CH(Me) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-Ph	
10	125	Me	CH(Et) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-Ph	
	126	Me	CH(Et) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-Ph	
	127	Me	CH(CH <sub>2</sub> OMe) cyclobutyl	2-Me-4-MeO-Ph	
	128	Me	CH(CH <sub>2</sub> OMe) cyclopropyl	2-Me-4-MeO-Ph	
	129	Me	CH(CH <sub>2</sub> OEt) cyclobutyl	2-Me-4-MeO-Ph	
15	130	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	2-Me-4-MeO-Ph	
	131	Me	CH(cyclobutyl) <sub>2</sub>	2-Me-4-MeO-Ph	
	132	Me	CH(cyclopropyl) <sub>2</sub>	2-Me-4-MeO-Ph	
	133	Me	CH(Et) CH <sub>2</sub> CONMe <sub>2</sub>	2-Me-4-MeO-Ph	
	134	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Me-4-MeO-Ph	
20	135	Me	CH(CH <sub>2</sub> OMe) Me	2-Me-4-MeO-Ph	
	136	Me	CH(CH <sub>2</sub> OMe) Et	2-Me-4-MeO-Ph	
	137	Me	CH(CH <sub>2</sub> OMe) Pr	2-Me-4-MeO-Ph	
	138	Me	CH(CH <sub>2</sub> OEt) Me	2-Me-4-MeO-Ph	
	139	Me	CH(CH <sub>2</sub> OEt) Et	2-Me-4-MeO-Ph	
25	140	Me	CH(CH <sub>2</sub> OEt) Pr	2-Me-4-MeO-Ph	
	141	Me	CH(CH <sub>2</sub> C≡CMe) Et	2-Me-4-MeO-Ph	
	142	Me	CH(CH <sub>2</sub> CH=CHMe) Et	2-Me-4-MeO-Ph	
	143	Me	CH(Et) CH <sub>2</sub> OH	2-Cl-4-MeO-Ph	
	144	Me	CH(Et) CH <sub>2</sub> OMe	2-Cl-4-MeO-Ph	
30	145	Me	CH(Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2-Cl-4-MeO-Ph	
	146	Me	3-pentyl	2-Cl-4-MeO-Ph	
	147	Me	2-pentyl	2-Cl-4-MeO-Ph	112-113
	148	Me	2-butyl	2-Cl-4-MeO-Ph	
	149	Me	cyclobutyl	2-Cl-4-MeO-Ph	
35	150	Me	cyclopentyl	2-Cl-4-MeO-Ph	

	151	Me	CH (Me) cyclobutyl	2-Cl-4-MeO-Ph
	152	Me	CH (Me) cyclopropyl	2-Cl-4-MeO-Ph
	153	Me	CH (Et) cyclobutyl	2-Cl-4-MeO-Ph
	154	Me	CH (Et) cyclopropyl	2-Cl-4-MeO-Ph
5	155	Me	CH (Me) CH <sub>2</sub> -cyclobutyl	2-Cl-4-MeO-Ph
	156	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2-Cl-4-MeO-Ph
	157	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2-Cl-4-MeO-Ph
	158	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2-Cl-4-MeO-Ph
	159	Me	CH (CH <sub>2</sub> OMe) cyclobutyl	2-Cl-4-MeO-Ph
10	160	Me	CH (CH <sub>2</sub> OMe) cyclopropyl	2-Cl-4-MeO-Ph
	161	Me	CH (CH <sub>2</sub> OEt) cyclobutyl	2-Cl-4-MeO-Ph
	162	Me	CH (CH <sub>2</sub> OEt) cyclopropyl	2-Cl-4-MeO-Ph
	163	Me	CH (cyclobutyl) <sub>2</sub>	2-Cl-4-MeO-Ph
	164	Me	CH (cyclopropyl) <sub>2</sub>	2-Cl-4-MeO-Ph
15	165	Me	CH (Et) CH <sub>2</sub> CONMe <sub>2</sub>	2-Cl-4-MeO-Ph
	166	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Cl-4-MeO-Ph
	167	Me	CH (CH <sub>2</sub> OMe) Me	2-Cl-4-MeO-Ph
	168	Me	CH (CH <sub>2</sub> OMe) Et	2-Cl-4-MeO-Ph
	169	Me	CH (CH <sub>2</sub> OMe) Pr	2-Cl-4-MeO-Ph
20	170	Me	CH (CH <sub>2</sub> OEt) Me	2-Cl-4-MeO-Ph
	171	Me	CH (CH <sub>2</sub> OEt) Et	2-Cl-4-MeO-Ph
	172	Me	CH (CH <sub>2</sub> OEt) Pr	2-Cl-4-MeO-Ph
	173	Me	CH (CH <sub>2</sub> C≡CMe) Et	2-Cl-4-MeO-Ph
	174	Me	CH (CH <sub>2</sub> CH=CHMe) Et	2-Cl-4-MeO-Ph
25	175	Me	CH (Et) CH <sub>2</sub> OH	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	176	Me	CH (Et) CH <sub>2</sub> OMe	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	177	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	178	Me	3-pentyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	179	Me	2-pentyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
30	180	Me	2-butyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	181	Me	cyclobutyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	182	Me	cyclopentyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	183	Me	CH (Me) cyclobutyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
	184	Me	CH (Me) cyclopropyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph
35	185	Me	CH (Et) cyclobutyl	2-Cl-4, 5- (MeO) <sub>2</sub> -Ph

	186	Me	CH(Et) cyclopropyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	187	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	188	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	189	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
<b>5</b>	190	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	191	Me	CH(CH <sub>2</sub> OMe) cyclobutyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	192	Me	CH(CH <sub>2</sub> OMe) cyclopropyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	193	Me	CH(CH <sub>2</sub> OEt) cyclobutyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	194	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
<b>10</b>	195	Me	CH(cyclobutyl) <sub>2</sub>	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	196	Me	CH(cyclopropyl) <sub>2</sub>	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	197	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	198	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	199	Me	CH(CH <sub>2</sub> OMe) Me	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
<b>15</b>	200	Me	CH(CH <sub>2</sub> OMe) Et	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	201	Me	CH(CH <sub>2</sub> OMe) Pr	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	202	Me	CH(CH <sub>2</sub> OEt) Me	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	203	Me	CH(CH <sub>2</sub> OEt) Et	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	204	Me	CH(CH <sub>2</sub> OEt) Pr	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
<b>20</b>	205	Me	CH(CH <sub>2</sub> C≡CMe) Et	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	206	Me	CH(CH <sub>2</sub> CH=CHMe) Et	2-Cl-4,5-(MeO) <sub>2</sub> -Ph
	207	Me	CH(Et)CH <sub>2</sub> OH	2-Cl-4-MeO-5-F-Ph
	208	Me	CH(Et)CH <sub>2</sub> OMe	2-Cl-4-MeO-5-F-Ph
	209	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	2-Cl-4-MeO-5-F-Ph
<b>25</b>	210	Me	3-pentyl	2-Cl-4-MeO-5-F-Ph
	211	Me	2-pentyl	2-Cl-4-MeO-5-F-Ph
	212	Me	2-butyl	2-Cl-4-MeO-5-F-Ph
	213	Me	cyclobutyl	2-Cl-4-MeO-5-F-Ph
	214	Me	cyclopentyl	2-Cl-4-MeO-5-F-Ph
<b>30</b>	215	Me	CH(Me) cyclobutyl	2-Cl-4-MeO-5-F-Ph
	216	Me	CH(Me) cyclopropyl	2-Cl-4-MeO-5-F-Ph
	217	Me	CH(Et) cyclobutyl	2-Cl-4-MeO-5-F-Ph
	218	Me	CH(Et) cyclopropyl	2-Cl-4-MeO-5-F-Ph
	219	Me	CH(OEt) cyclobutyl	2-Cl-4-MeO-5-F-Ph
<b>35</b>	220	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2-Cl-4-MeO-5-F-Ph

	221	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2-Cl-4-MeO-5-F-Ph
	222	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2-Cl-4-MeO-5-F-Ph
	223	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2-Cl-4-MeO-5-F-Ph
	224	Me	CH (CH <sub>2</sub> OMe) cyclobutyl	2-Cl-4-MeO-5-F-Ph
5	225	Me	CH (CH <sub>2</sub> OMe) cyclopropyl	2-Cl-4-MeO-5-F-Ph
	226	Me	CH (CH <sub>2</sub> OEt) cyclobutyl	2-Cl-4-MeO-5-F-Ph
	227	Me	CH (CH <sub>2</sub> OEt) cyclopropyl	2-Cl-4-MeO-5-F-Ph
	228	Me	CH (cyclobutyl) <sub>2</sub>	2-Cl-4-MeO-5-F-Ph
	229	Me	CH (cyclopropyl) <sub>2</sub>	2-Cl-4-MeO-5-F-Ph
10	230	Me	CH (Et) CH <sub>2</sub> CONMe <sub>2</sub>	2-Cl-4-MeO-5-F-Ph
	231	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Cl-4-MeO-5-F-Ph
	232	Me	CH (CH <sub>2</sub> OMe) Me	2-Cl-4-MeO-5-F-Ph
	233	Me	CH (CH <sub>2</sub> OMe) Et	2-Cl-4-MeO-5-F-Ph
	234	Me	CH (CH <sub>2</sub> OMe) Pr	2-Cl-4-MeO-5-F-Ph
15	234	Me	CH (CH <sub>2</sub> OEt) Me	2-Cl-4-MeO-5-F-Ph
	235	Me	CH (CH <sub>2</sub> OEt) Et	2-Cl-4-MeO-5-F-Ph
	236	Me	CH (CH <sub>2</sub> OEt) Pr	2-Cl-4-MeO-5-F-Ph
	237	Me	CH (CH <sub>2</sub> C=Me) Et	2-Cl-4-MeO-5-F-Ph
	238	Me	CH (CH <sub>2</sub> CH=CHMe) Et	2-Cl-4-MeO-5-F-Ph
20	239	Me	CH (Et) CH <sub>2</sub> OH	2-Me-4-MeO-5-F-Ph
	240	Me	CH (Et) CH <sub>2</sub> OMe	2-Me-4-MeO-5-F-Ph
	241	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2-Me-4-MeO-5-F-Ph
	242	Me	3-pentyl	2-Me-4-MeO-5-F-Ph
	243	Me	2-pentyl	2-Me-4-MeO-5-F-Ph
25	244	Me	2-butyl	2-Me-4-MeO-5-F-Ph
	245	Me	cyclobutyl	2-Me-4-MeO-5-F-Ph
	246	Me	cyclopentyl	2-Me-4-MeO-5-F-Ph
	247	Me	CH (Me) cyclobutyl	2-Me-4-MeO-5-F-Ph
	248	Me	CH (Me) cyclopropyl	2-Me-4-MeO-5-F-Ph
30	249	Me	CH (OMe) cyclopropyl	2-Me-4-MeO-5-F-Ph
	250	Me	CH (Et) cyclobutyl	2-Me-4-MeO-5-F-Ph
	251	Me	CH (Et) cyclopropyl	2-Me-4-MeO-5-F-Ph
	252	Me	CH (Me) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph
	253	Me	CH (OMe) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph
35	254	Me	CH (OH) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph

	255	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-5-F-Ph
	256	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph
	257	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-5-F-Ph
	258	Me	CH (OMe) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph
5	259	Me	CH (OMe) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-5-F-Ph
	260	Me	CH (OEt) CH <sub>2</sub> -cyclobutyl	2-Me-4-MeO-5-F-Ph
	261	Me	CH (OEt) CH <sub>2</sub> -cyclopropyl	2-Me-4-MeO-5-F-Ph
	262	Me	CH (CH <sub>2</sub> OMe) cyclobutyl	2-Me-4-MeO-5-F-Ph
	263	Me	CH (CH <sub>2</sub> OMe) cyclopropyl	2-Me-4-MeO-5-F-Ph
10	264	Me	CH (CH <sub>2</sub> OEt) cyclobutyl	2-Me-4-MeO-5-F-Ph
	265	Me	CH (CH <sub>2</sub> OEt) cyclopropyl	2-Me-4-MeO-5-F-Ph
	266	Me	CH (cyclobutyl) <sub>2</sub>	2-Me-4-MeO-5-F-Ph
	267	Me	CH (cyclopropyl) <sub>2</sub>	2-Me-4-MeO-5-F-Ph
	268	Me	CH (Et) CH <sub>2</sub> CONMe <sub>2</sub>	2-Me-4-MeO-5-F-Ph
15	269	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Me-4-MeO-5-F-Ph
	270	Me	CH (CH <sub>2</sub> OMe) Me	2-Me-4-MeO-5-F-Ph
	271	Me	CH (CH <sub>2</sub> OMe) Et	2-Me-4-MeO-5-F-Ph
	272	Me	CH (CH <sub>2</sub> OMe) Pr	2-Me-4-MeO-5-F-Ph
	273	Me	CH (CH <sub>2</sub> OEt) Me	2-Me-4-MeO-5-F-Ph
20	274	Me	CH (CH <sub>2</sub> OEt) Et	2-Me-4-MeO-5-F-Ph
	275	Me	CH (CH <sub>2</sub> OEt) Pr	2-Me-4-MeO-5-F-Ph
	276	Me	CH (CH <sub>2</sub> C≡CMe) Et	2-Me-4-MeO-5-F-Ph
	277	Me	CH (CH <sub>2</sub> C≡CMe) Et	2-Me-4-MeO-5-F-Ph
	278	Me	CH (Et) CH <sub>2</sub> OH	2,5-(Me) <sub>2</sub> -4-MeO-Ph
25	279	Me	CH (Et) CH <sub>2</sub> OMe	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	280	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	281	Me	3-pentyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	282	Me	2-butyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	283	Me	cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
30	284	Me	cyclopentyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	285	Me	CH (Me) cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	286	Me	CH (Me) cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	287	Me	CH (Et) cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	288	Me	CH (Et) cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
35	289	Me	CH (Me) CH <sub>2</sub> -cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph

	290	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	291	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	292	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	293	Me	CH (CH <sub>2</sub> OMe) cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
5	294	Me	CH (CH <sub>2</sub> OMe) cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	295	Me	CH (CH <sub>2</sub> OEt) cyclobutyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	296	Me	CH (CH <sub>2</sub> OEt) cyclopropyl	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	297	Me	CH (cyclobutyl) <sub>2</sub>	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	298	Me	CH (cyclopropyl) <sub>2</sub>	2,5-(Me) <sub>2</sub> -4-MeO-Ph
10	299	Me	CH (Et) CH <sub>2</sub> CONMe <sub>2</sub>	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	300	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	301	Me	CH (CH <sub>2</sub> OMe) Me	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	302	Me	CH (CH <sub>2</sub> OMe) Et	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	303	Me	CH (CH <sub>2</sub> OMe) Pr	2,5-(Me) <sub>2</sub> -4-MeO-Ph
15	304	Me	CH (CH <sub>2</sub> OEt) Me	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	305	Me	CH (CH <sub>2</sub> OEt) Et	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	306	Me	CH (CH <sub>2</sub> OEt) Pr	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	307	Me	CH (CH <sub>2</sub> C≡CMe) Et	2,5-(Me) <sub>2</sub> -4-MeO-Ph
	308	Me	CH (CH <sub>2</sub> CH=CHMe) Et	2,5-(Me) <sub>2</sub> -4-MeO-Ph
20	309	Me	CH (Et) CH <sub>2</sub> OH	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	310	Me	CH (Et) CH <sub>2</sub> OMe	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	311	Me	CH (Et) CH <sub>2</sub> CH <sub>2</sub> OMe	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	312	Me	3-pentyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	313	Me	2-pentyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
25	314	Me	2-butyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	315	Me	cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	316	Me	cyclopentyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	317	Me	CH (Me) cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	318	Me	CH (Me) cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
30	319	Me	CH (Et) cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	320	Me	CH (Et) cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	321	Me	CH (Me) CH <sub>2</sub> -cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	322	Me	CH (Me) CH <sub>2</sub> -cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	323	Me	CH (Et) CH <sub>2</sub> -cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
35	324	Me	CH (Et) CH <sub>2</sub> -cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl

	325	Me	CH(CH <sub>2</sub> OMe) cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	326	Me	CH(CH <sub>2</sub> OMe) cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	327	Me	CH(CH <sub>2</sub> OEt) cyclobutyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	328	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
5	329	Me	CH(cyclobutyl) <sub>2</sub>	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	330	Me	CH(cyclopropyl) <sub>2</sub>	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	331	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	332	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	333	Me	CH(CH <sub>2</sub> OMe)Me	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
10	334	Me	CH(CH <sub>2</sub> OMe)Et	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	335	Me	CH(CH <sub>2</sub> OMe)Pr	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	336	Me	CH(CH <sub>2</sub> OEt)Me	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	337	Me	CH(CH <sub>2</sub> OEt)Et	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	338	Me	CH(CH <sub>2</sub> OEt)Pr	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
15	339	Me	CH(CH <sub>2</sub> C≡CMe)Et	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	340	Me	CH(CH <sub>2</sub> CH=CHMe)Et	2-Me-6-Me <sub>2</sub> N-pyrid-3-yl
	341	Me	CH(Et)CH <sub>2</sub> OH	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	342	Me	CH(Et)CH <sub>2</sub> OMe	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	343	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
20	344	Me	3-pentyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	345	Me	2-pentyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	346	Me	2-butyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	347	Me	cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	348	Me	cyclopentyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
25	349	Me	CH(Me)cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	350	Me	CH(Me)cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	351	Me	CH(Et)cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	352	Me	CH(Et)cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	353	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
30	354	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	355	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	356	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	357	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	358	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
35	359	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl

	360	Me	CH(CH <sub>2</sub> OEt) cyclopropyl	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	361	Me	CH(cyclobutyl) <sub>2</sub>	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	362	Me	CH(cyclopropyl) <sub>2</sub>	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	363	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
5	364	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	365	Me	CH(CH <sub>2</sub> OMe)Me	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	366	Me	CH(CH <sub>2</sub> OMe)Et	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	367	Me	CH(CH <sub>2</sub> OMe)Pr	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	368	Me	CH(CH <sub>2</sub> OEt)Me	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
10	369	Me	CH(CH <sub>2</sub> OEt)Et	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	370	Me	CH(CH <sub>2</sub> OEt)Pr	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	371	Me	CH(CH <sub>2</sub> C≡CMe)Et	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	372	Me	CH(CH <sub>2</sub> CH=CHMe)Et	4-Me-2-Me <sub>2</sub> N-pyrid-5-yl
	373	Me	CH(Et)CH <sub>2</sub> OH	2-Me-6-MeO-pyrid-3-yl
15	374	Me	CH(Et)CH <sub>2</sub> OMe	2-Me-6-MeO-pyrid-3-yl
	375	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	2-Me-6-MeO-pyrid-3-yl
	376	Me	3-pentyl	2-Me-6-MeO-pyrid-3-yl
	377	Me	2-pentyl	2-Me-6-MeO-pyrid-3-yl
	378	Me	2-butyl	2-Me-6-MeO-pyrid-3-yl
20	379	Me	cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	380	Me	cyclopentyl	2-Me-6-MeO-pyrid-3-yl
	381	Me	CH(Me)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	382	Me	CH(Me)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
	383	Me	CH(Et)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
25	384	Me	CH(Et)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
	385	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	386	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	2-Me-6-MeO-pyrid-3-yl
	387	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	388	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	2-Me-6-MeO-pyrid-3-yl
30	389	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	390	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
	391	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
	392	Me	CH(CH <sub>2</sub> OEt)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
	393	Me	CH(cyclobutyl) <sub>2</sub>	2-Me-6-MeO-pyrid-3-yl
35	394	Me	CH(cyclopropyl) <sub>2</sub>	2-Me-6-MeO-pyrid-3-yl



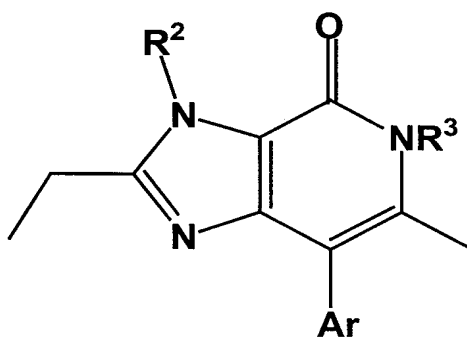
	395	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2-Me-6-MeO-pyrid-3-yl
	396	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2-Me-6-MeO-pyrid-3-yl
	397	Me	CH(CH <sub>2</sub> OMe)Me	2-Me-6-MeO-pyrid-3-yl
	398	Me	CH(CH <sub>2</sub> OMe)Et	2-Me-6-MeO-pyrid-3-yl
<b>5</b>	399	Me	CH(CH <sub>2</sub> OMe)Pr	2-Me-6-MeO-pyrid-3-yl
	400	Me	CH(CH <sub>2</sub> OEt)Me	2-Me-6-MeO-pyrid-3-yl
	401	Me	CH(CH <sub>2</sub> OEt)Et	2-Me-6-MeO-pyrid-3-yl
	402	Me	CH(CH <sub>2</sub> OEt)Pr	2-Me-6-MeO-pyrid-3-yl
	403	Me	CH(CH <sub>2</sub> C≡CMe)Et	2-Me-6-MeO-pyrid-3-yl
<b>10</b>	404	Me	CH(CH <sub>2</sub> CH=CHMe)Et	2-Me-6-MeO-pyrid-3-yl
	405	Me	CH(Et)CH <sub>2</sub> OH	4-Me-2-MeO-pyrid-5-yl
	406	Me	CH(Et)CH <sub>2</sub> OMe	4-Me-2-MeO-pyrid-5-yl
	407	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	4-Me-2-MeO-pyrid-5-yl
	408	Me	3-pentyl	4-Me-2-MeO-pyrid-5-yl
<b>15</b>	409	Me	2-pentyl	4-Me-2-MeO-pyrid-5-yl
	410	Me	2-butyl	4-Me-2-MeO-pyrid-5-yl
	411	Me	cyclobutyl	4-Me-2-MeO-pyrid-5-yl
	412	Me	cyclopentyl	4-Me-2-MeO-pyrid-5-yl
	413	Me	CH(Me)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
<b>20</b>	414	Me	CH(Me)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
	415	Me	CH(Et)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
	416	Me	CH(Et)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
	417	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	4-Me-2-MeO-pyrid-5-yl
	418	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	4-Me-2-MeO-pyrid-5-yl
<b>25</b>	419	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	4-Me-2-MeO-pyrid-5-yl
	420	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	4-Me-2-MeO-pyrid-5-yl
	421	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
	422	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
	423	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
<b>30</b>	424	Me	CH(CH <sub>2</sub> OEt)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
	425	Me	CH(cyclobutyl) <sub>2</sub>	4-Me-2-MeO-pyrid-5-yl
	426	Me	CH(cyclopropyl) <sub>2</sub>	4-Me-2-MeO-pyrid-5-yl
	427	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	4-Me-2-MeO-pyrid-5-yl
	428	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	4-Me-2-MeO-pyrid-5-yl
<b>35</b>	429	Me	CH(CH <sub>2</sub> OMe)Me	4-Me-2-MeO-pyrid-5-yl

	430	Me	CH(CH <sub>2</sub> OMe) Et	4-Me-2-MeO-pyrid-5-yl	
	431	Me	CH(CH <sub>2</sub> OMe) Pr	4-Me-2-MeO-pyrid-5-yl	
	432	Me	CH(CH <sub>2</sub> OEt) Me	4-Me-2-MeO-pyrid-5-yl	
	433	Me	CH(CH <sub>2</sub> OEt) Et	4-Me-2-MeO-pyrid-5-yl	
<b>5</b>	434	Me	CH(CH <sub>2</sub> OEt) Pr	4-Me-2-MeO-pyrid-5-yl	
	435	Me	CH(CH <sub>2</sub> C≡CMe) Et	4-Me-2-MeO-pyrid-5-yl	
	436	Me	CH(CH <sub>2</sub> CH=CHMe) Et	4-Me-2-MeO-pyrid-5-yl	
	536	H	2-pentyl	2,4-Cl <sub>2</sub> -5-F-Ph	159-160
	537	Me	2-pentyl	2,4-Cl <sub>2</sub> -5-F-Ph	120-121
<b>10</b>	538	Me	(R)-2-butyl	2,4-Cl <sub>2</sub> -Ph	105-107
	539	Me	(S)-2-butyl	2,4-Cl <sub>2</sub> -Ph	oil
	540	Me	2-pentyl	4-Br-2-Cl-Ph	97-98
	541	Me	2-pentyl	Ph	oil
	542	Me	2-pentyl	4-OMe-Ph	oil
<b>15</b>	543	Me	CH <sub>2</sub> OCH <sub>2</sub> Ph	2,4-Cl <sub>2</sub> -Ph	oil
	544	Me	H	2,4-Cl <sub>2</sub> -Ph	234-235
	545	H	CH <sub>2</sub> OCH <sub>2</sub> Ph	2,4-Cl <sub>2</sub> -Ph	174-175
	546	Me	n-butyl	2,4-Cl <sub>2</sub> -Ph	oil
	547	Me	CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	oil
<b>20</b>	548	Me	3-heptyl	2,4-Cl <sub>2</sub> -Ph	110-111
	549	Me	(S)-2-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	550	Me	(R)-2-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	551	Me	CH(Et)CH <sub>2</sub> C≡CH	2,4-Cl <sub>2</sub> -Ph	oil
	552	Me	2-hexyl	2,4-Cl <sub>2</sub> -Ph	oil
<b>25</b>	553	Me	3-hexyl	2,4-Cl <sub>2</sub> -Ph	135-136
	554	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> CH=CH <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	106-107
	555	Me	CH(CH <sub>2</sub> CH=CH <sub>2</sub> ) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	oil
	556	Me	CH(Me)CH <sub>2</sub> OCH <sub>3</sub>	2,4-Cl <sub>2</sub> -Ph	oil
	557	Me	CH(n-C <sub>3</sub> H <sub>7</sub> )-cyclopropyl	2,4-Cl <sub>2</sub> -Ph	139-140
<b>30</b>	558	Me	CH(Ph)-cyclopropyl	2,4-Cl <sub>2</sub> -Ph	172-173
	559	Me	CH(4-OMe-Ph)-cyclopropyl	2,4-Cl <sub>2</sub> -Ph	oil
	560	Me	CH(4-Me-Ph)-cyclopropyl	2,4-Cl <sub>2</sub> -Ph	oil
	561	Me	CH(4-F-Ph)-cyclopropyl	2,4-Cl <sub>2</sub> -Ph	oil
	562	Me	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	oil
<b>35</b>	563	Me	CH <sub>2</sub> C(=CH <sub>2</sub> )Me	2,4-Cl <sub>2</sub> -Ph	126-127

	564	Me	$\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	2,4-Cl <sub>2</sub> -Ph	105-106
	565	Me	$\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	2,4-Cl <sub>2</sub> -Ph	oil
	566	Me	$\text{CH}_2\text{C}\equiv\text{CMe}$	2,4-Cl <sub>2</sub> -Ph	148-149
	567	Me	(R) - $\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$	2,4-Cl <sub>2</sub> -Ph	oil
5	568	Me	(S) - $\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$	2,4-Cl <sub>2</sub> -Ph	oil
	569	Me	$\text{CH}_2\text{COCH}_2\text{CH}_3$	2,4-Cl <sub>2</sub> -Ph	104-105
	570	Me	$\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$	2,4-Cl <sub>2</sub> -Ph	oil
	571	Me	n-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	572	Me	$\text{CH}_2(\text{CH}_2)_2\text{CH}=\text{CH}_2$	2,4-Cl <sub>2</sub> -Ph	oil
10	573	Me	$\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_3$	2,4-Cl <sub>2</sub> -Ph	oil
	574	Me	$\text{CH}_2(2\text{-Cl-Ph})$	2,4-Cl <sub>2</sub> -Ph	163-165
	575	Me	$\text{CH}_2(3\text{-Cl-Ph})$	2,4-Cl <sub>2</sub> -Ph	82-84
	576	Me	$\text{CH}_2(4\text{-Cl-Ph})$	2,4-Cl <sub>2</sub> -Ph	149-150
	577	Me	$\text{CH}_2(2,4\text{-Cl}_2\text{-Ph})$	2,4-Cl <sub>2</sub> -Ph	85-87
15	578	Me	$\text{CH}_2(2,4\text{-F}_2\text{-Ph})$	2,4-Cl <sub>2</sub> -Ph	oil
	579	Me	$\text{CH}(\text{Me})\text{Ph}$	2,4-Cl <sub>2</sub> -Ph	179-180
	580	Me	$\text{CH}_2\text{CH}_2\text{Ph}$	2,4-Cl <sub>2</sub> -Ph	oil
	581	Me	$\text{CH}_2\text{-cyclobutyl}$	2,4-Cl <sub>2</sub> -Ph	oil
	582	Me	2-pentyl	2-4-CF <sub>3</sub> -Ph	oil
20	583	Me	2-pentyl	2-Cl-4-F-Ph	oil
	584	Me	2-pentyl	2,4-Cl <sub>2</sub> -Ph	oil
	585	Me	2-pentyl	2,6-(OMe) <sub>2</sub> -pyrid-5-yl	oil

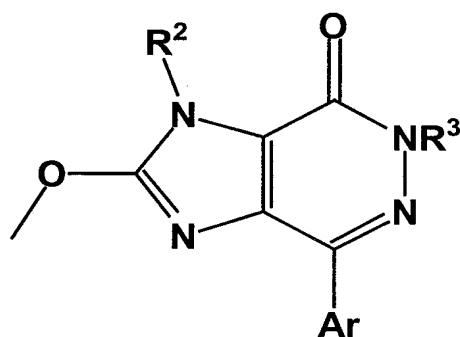
Table 2

25



<u>Ex.</u>	<u>R<sub>3</sub></u>	<u>R<sub>2</sub></u>	<u>Ar</u>	<u>mp (°C)</u>
5	437	Me	CH(Et)CH <sub>2</sub> OH	2,4-Cl <sub>2</sub> -Ph
	438	Me	CH(Et)CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph
	439	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph
	440	Me	3-pentyl	2,4-Cl <sub>2</sub> -Ph
	441	Me	2-pentyl	2,4-Cl <sub>2</sub> -Ph
10	442	Me	2-butyl	2,4-Cl <sub>2</sub> -Ph
	443	Me	cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	444	Me	cyclopentyl	2,4-Cl <sub>2</sub> -Ph
	445	Me	CH(Me)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	446	Me	CH(Me)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
15	447	Me	CH(Et)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	448	Me	CH(Et)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	449	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	450	Me	CH(OH)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	451	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph
20	452	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	453	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	454	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	455	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	456	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
25	457	Me	CH(CH <sub>2</sub> OEt)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	458	Me	CH(cyclobutyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	459	Me	CH(cyclopropyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	460	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	461	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
30	462	Me	CH(CH <sub>2</sub> OMe)Me	2,4-Cl <sub>2</sub> -Ph
	463	Me	CH(CH <sub>2</sub> OMe)Et	2,4-Cl <sub>2</sub> -Ph
	464	Me	CH(CH <sub>2</sub> OMe)Pr	2,4-Cl <sub>2</sub> -Ph
	465	Me	CH(CH <sub>2</sub> OEt)Me	2,4-Cl <sub>2</sub> -Ph
	466	Me	CH(CH <sub>2</sub> OEt)Et	2,4-Cl <sub>2</sub> -Ph
35	467	Me	CH(CH <sub>2</sub> OEt)Pr	2,4-Cl <sub>2</sub> -Ph
	468	Me	CH(CH <sub>2</sub> C≡CMe)Et	2,4-Cl <sub>2</sub> -Ph
	469	Me	CH(CH <sub>2</sub> CH=CHMe)Et	2,4-Cl <sub>2</sub> -Ph

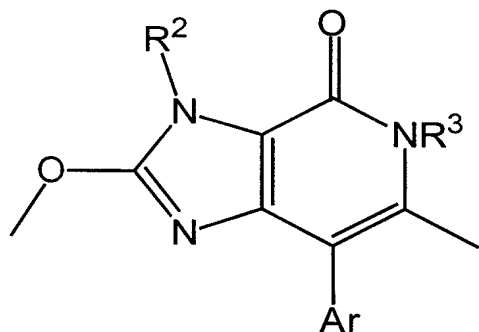
Table 3



5	<u>Ex.</u>	<u>R<sub>3</sub></u>	<u>R<sub>2</sub></u>	<u>Ar</u>	<u>mp (°C)</u>
	470	Me	CH(Et)CH <sub>2</sub> OH	2,4-Cl <sub>2</sub> -Ph	
	471	Me	CH(Et)CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
	472	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
10	473	Me	3-pentyl	2,4-Cl <sub>2</sub> -Ph	
	474	Me	2-pentyl	2,4-Cl <sub>2</sub> -Ph	
	475	Me	2-butyl	2,4-Cl <sub>2</sub> -Ph	
	476	Me	cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	477	Me	cyclopentyl	2,4-Cl <sub>2</sub> -Ph	
15	478	Me	CH(Me)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	479	Me	CH(Me)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	480	Me	CH(Et)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	481	Me	CH(Et)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	482	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
20	483	Me	CH(OH)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	484	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	485	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	486	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	487	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
25	488	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	489	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	490	Me	CH(CH <sub>2</sub> OEt)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	491	Me	CH(cyclobutyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	
	492	Me	CH(cyclopropyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph	

	493	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	494	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	495	Me	CH(CH <sub>2</sub> OMe)Me	2,4-Cl <sub>2</sub> -Ph
	496	Me	CH(CH <sub>2</sub> OMe)Et	2,4-Cl <sub>2</sub> -Ph
5	497	Me	CH(CH <sub>2</sub> OMe)Pr	2,4-Cl <sub>2</sub> -Ph
	498	Me	CH(CH <sub>2</sub> OEt)Me	2,4-Cl <sub>2</sub> -Ph
	499	Me	CH(CH <sub>2</sub> OEt)Et	2,4-Cl <sub>2</sub> -Ph
	500	Me	CH(CH <sub>2</sub> OEt)Pr	2,4-Cl <sub>2</sub> -Ph
	501	Me	CH(CH <sub>2</sub> C≡CMe)Et	2,4-Cl <sub>2</sub> -Ph
10	502	Me	CH(CH <sub>2</sub> C≡CMe)Et	2,4-Cl <sub>2</sub> -Ph

Table 4



	<u>Ex.</u>	<u>R<sub>3</sub></u>	<u>R<sub>2</sub></u>	<u>Ar</u>	<u>mp (°C)</u>
15					
	503	Me	CH(Et)CH <sub>2</sub> OH	2,4-Cl <sub>2</sub> -Ph	
	504	Me	CH(Et)CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
	505	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> OMe	2,4-Cl <sub>2</sub> -Ph	
	506	Me	3-pentyl	2,4-Cl <sub>2</sub> -Ph	
20	507	Me	2-pentyl	2,4-Cl <sub>2</sub> -Ph	
	508	Me	2-butyl	2,4-Cl <sub>2</sub> -Ph	
	509	Me	cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	510	Me	cyclopentyl	2,4-Cl <sub>2</sub> -Ph	
	511	Me	CH(Me)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
25	512	Me	CH(Me)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	513	Me	CH(Et)cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	514	Me	CH(Et)cyclopropyl	2,4-Cl <sub>2</sub> -Ph	
	515	Me	CH(Me)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	
	516	Me	CH(OH)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph	

	517	Me	CH(Me)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	518	Me	CH(Et)CH <sub>2</sub> -cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	519	Me	CH(Et)CH <sub>2</sub> -cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	520	Me	CH(CH <sub>2</sub> OMe)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
5	521	Me	CH(CH <sub>2</sub> OMe)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	522	Me	CH(CH <sub>2</sub> OEt)cyclobutyl	2,4-Cl <sub>2</sub> -Ph
	523	Me	CH(CH <sub>2</sub> OEt)cyclopropyl	2,4-Cl <sub>2</sub> -Ph
	524	Me	CH(cyclobutyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	525	Me	CH(cyclopropyl) <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
10	526	Me	CH(Et)CH <sub>2</sub> CONMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	527	Me	CH(Et)CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	2,4-Cl <sub>2</sub> -Ph
	528	Me	CH(CH <sub>2</sub> OMe)Me	2,4-Cl <sub>2</sub> -Ph
	529	Me	CH(CH <sub>2</sub> OMe)Et	2,4-Cl <sub>2</sub> -Ph
	530	Me	CH(CH <sub>2</sub> OMe)Pr	2,4-Cl <sub>2</sub> -Ph
15	531	Me	CH(CH <sub>2</sub> OEt)Me	2,4-Cl <sub>2</sub> -Ph
	532	Me	CH(CH <sub>2</sub> OEt)Et	2,4-Cl <sub>2</sub> -Ph
	533	Me	CH(CH <sub>2</sub> OEt)Pr	2,4-Cl <sub>2</sub> -Ph
	534	Me	CH(CH <sub>2</sub> C≡CMe)Et	2,4-Cl <sub>2</sub> -Ph
	535	Me	CH(CH <sub>2</sub> CH=CHMe)Et	2,4-Cl <sub>2</sub> -Ph

20

Examples shown above in Tables 1-4 wherein R<sup>3</sup> is H, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, or C<sub>1-6</sub>alkylC<sub>3-6</sub> cycloalkyl are also readily prepared according to the procedures disclosed herein.

25

#### CRF Receptor Binding Assay for the Evaluation of Biological Activity

##### *Radioligand binding experiments*

30

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had K<sub>i</sub>s of 10,000 nM or less and are thus useful as CRF receptor antagonists. Preferred antagonists have or will have a K<sub>i</sub> of 1,000 nM or less. Radioligand binding experiments were

35

performed with membranes from rat frontal cortex to determine binding affinities ( $K_i$ 's) of test compounds for the rat CRH<sub>1</sub> receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM MgCl<sub>2</sub>, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [<sup>125</sup>I] tyr<sup>o</sup> ovine CRH; New England Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10<sup>-11</sup> to 1 X 10<sup>-5</sup> M). The reactions mixtures were incubated to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly



washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

- 5 Binding affinities ( $K_i$ 's) of ligands for the  $CRH_1$  receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition  
10 equation.

#### Inhibition of CRF-Stimulated Adenylate Cyclase Activity

- Inhibition of CRF-stimulated adenylate cyclase  
15 activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37°C for 10 min in 200  $\mu$ l of buffer containing 100 mM Tris-HCl (pH 7.4 at 37°C), 10 mM  $MgCl_2$ , 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250  
20 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range  $10^{-9}$  to  $10^{-6}$  M) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1  
25 mM ATP/ $^{32}P$ ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100  $\mu$ l of 50 mM Tris-HCl, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1  $\mu$ l of [ $^3H$ ]cAMP (approximately 40,000 dpm) is added to each tube prior to  
30 separation. The separation of [ $^{32}P$ ]cAMP from [ $^{32}P$ ]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990). Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally

administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be  
5 effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical  
10 compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and  
15 powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active  
20 ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for  
25 continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal  
30 tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable  
35 oils, saline, aqueous dextrose (glucose), and related

sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

#### Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

#### Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

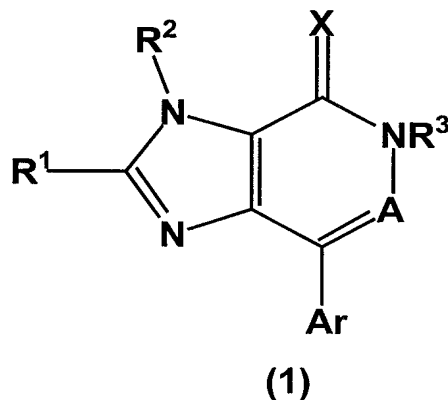
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon  
5 dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

10 The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described  
15 and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation  
20 without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (1):



- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

10

X is O or S;

A = N or CR<sup>9</sup>;

15

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R<sup>4</sup> groups and each Ar is attached via an unsaturated carbon atom;

20

25 R<sup>1</sup> is independently selected at each occurrence from H, C<sub>1</sub>-C<sub>4</sub>†alkyl, C<sub>2</sub>-C<sub>4</sub>†alkenyl, C<sub>2</sub>-C<sub>4</sub>†alkynyl, halo, CN, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, C<sub>1</sub>-C<sub>12</sub> hydroxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>10</sub> cyanoalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,

C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, NR<sup>9</sup>R<sup>10</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sup>9</sup>R<sup>10</sup>,  
NR<sup>9</sup>COR<sup>10</sup>, OR<sup>11</sup>, SH or S(O)<sub>n</sub>R<sup>12</sup>;

R<sup>2</sup> is selected from:

- 5        -H, aryl, heteroaryl and heterocyclyl,  
         or  
         -C<sub>1</sub>-C<sub>10</sub>+alkyl, C<sub>2</sub>-C<sub>10</sub>+alkenyl, C<sub>2</sub>-C<sub>10</sub>+alkynyl, C<sub>3</sub>-  
         C<sub>8</sub>+cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-  
         C<sub>12</sub>+cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkenylalkyl,  
10        each optionally substituted with 1 to 3  
         substituents independently selected at each  
         occurrence from C<sub>1</sub>-C<sub>6</sub>+alkyl, C<sub>1</sub>-<sub>6</sub> alkyloxy-C<sub>1</sub>-<sub>6</sub>  
         alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkynyl, C<sub>3</sub>-  
         C<sub>6</sub>+cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>+haloalkyl, cyano, OR<sup>15</sup>,  
15        SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>,  
         N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>,  
         CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and heterocyclyl;

R<sup>3</sup> is selected from:

- 20        -H, aryl, heteroaryl and heterocyclyl,  
         or  
         C<sub>1</sub>-C<sub>4</sub>+alkyl, C<sub>3</sub>-C<sub>6</sub>+alkenyl, C<sub>3</sub>-C<sub>6</sub>+alkynyl, C<sub>3</sub>-  
         C<sub>6</sub>+cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, each  
         optionally substituted with 1 to 3 substituents  
25        independently selected at each occurrence from C<sub>1</sub>-  
         C<sub>6</sub>+alkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>+haloalkyl,  
         cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>,  
         NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>,  
         NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and  
30        heterocyclyl;

R<sup>4</sup> is independently selected at each occurrence from: C<sub>1</sub>-

- C<sub>10</sub>+alkyl, C<sub>2</sub>-C<sub>10</sub>+alkenyl, C<sub>2</sub>-C<sub>10</sub>+alkynyl, C<sub>3</sub>-C<sub>6</sub>  
         cycloalkyl, C<sub>4</sub>-C<sub>12</sub>+cycloalkylalkyl, NO<sub>2</sub>, halo, CN,  
35        C<sub>1</sub>-C<sub>4</sub>+haloalkyl, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>, COR<sup>7</sup>,

- OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, CO(NOR<sup>9</sup>)R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, or S(O)<sub>n</sub>R<sup>7</sup>, where each such C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl are optionally substituted with
- 5 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>4</sub> alkyl, NO<sub>2</sub>, halo, CN, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>, COR<sup>7</sup> OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CO(NOR<sup>9</sup>)R<sup>7</sup>, or S(O)<sub>n</sub>R<sup>7</sup>;
- 10 R<sup>6</sup> and R<sup>7</sup> are independently selected at each occurrence from:
- H,
- C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>10</sub> haloalkyl with 1-10 halogens, C<sub>2</sub>-C<sub>8</sub>
- 15 alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl, C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, or C<sub>6</sub>-C<sub>14</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from
- 20 C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl or heterocyclyl,
- 25 -aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl, heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl or heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl);
- 30 alternatively, NR<sup>6</sup>R<sup>7</sup> is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C<sub>1</sub>-C<sub>4</sub> alkyl groups;



- $R^8$  is independently selected at each occurrence from H or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted by halogen, C<sub>1</sub>-C<sub>4</sub> alkoxy or C<sub>1</sub>-C<sub>4</sub> halo-alkoxy (1 to 4 halogens);
- 5  $R^9$  and  $R^{10}$  are independently selected at each occurrence from H, C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- $R^{11}$  is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- 10  $R^{12}$  is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- $R^{13}$  is selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, C<sub>4</sub>-C<sub>12</sub>+cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-, heteroaryl or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;
- 15  $R^{15}$  and  $R^{16}$  are independently selected at each occurrence from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>16</sub> cycloalkylalkyl, except that for S(O)<sub>n</sub> $R^{15}$ ,  $R^{15}$  cannot be H;
- 20 aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>+alkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>+haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub> $R^{15}$ , COR<sup>15</sup>, CO<sub>2</sub> $R^{15}$ , OC(O) $R^{15}$ , NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup> $R^{15}$ , NR<sup>8</sup>CO<sub>2</sub> $R^{15}$ , NR<sup>16</sup> $R^{15}$ , and CONR<sup>16</sup> $R^{15}$ ;
- 25 heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally
- 30  
35

substituted with 1 to 5 substituents independently  
 selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-  
 C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>,  
 SH, S(O)<sub>n</sub>R<sup>15</sup>, -COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>,  
 5 N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>16</sup>R<sup>15</sup>, and  
 CONR<sup>16</sup>R<sup>15</sup>;

heterocyclyl is saturated or partially saturated  
 heteroaryl, optionally substituted with 1 to 5  
 10 substituents independently selected at each  
 occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl,  
 halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>15</sup>,  
 COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>,  
 NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, and CONR<sup>16</sup>R<sup>15</sup>;

15 n is independently at each occurrence 0, 1 or 2.

2. The compound according to claim 1 wherein Ar is  
 phenyl or pyridyl, each optionally substituted with  
 20 1 to 4 R<sup>4</sup> substituents.

3. The compound according to claim 1 wherein Ar is  
 phenyl wherein phenyl is optionally substituted  
 with 1 to 3 R<sup>4</sup> substituents.

25 4. The compound according to claim 1 wherein R<sup>2</sup> is:

- C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-  
 C<sub>8</sub>†cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-  
 30 C<sub>12</sub>†cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub>  
 cycloalkenylalkyl, each optionally  
 substituted with 1 to 3 substituents  
 independently selected at each occurrence  
 from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo,  
 35 C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH,

$S(O)_nR^{13}$ ,  $COR^{15}$ ,  $CO_2R^{15}$ ,  $OC(O)R^{13}$ ,  
 $NR^8COR^{15}$ ,  $N(COR^{15})_2$ ,  $NR^8CONR^{16}R^{15}$ ,  
 $NR^8CO_2R^{13}$ ,  $NR^{16}R^{15}$ ,  $CONR^{16}R^{15}$ , aryl,  
heteroaryl and heterocyclyl.

5

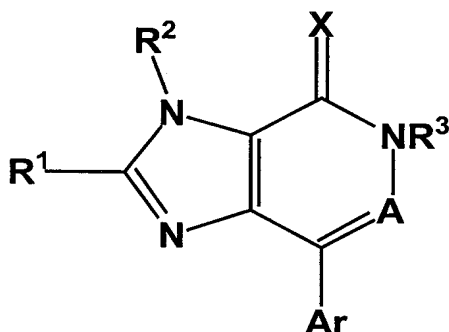
5. The compound according to claim 1 wherein  $R^1$ ,  $R^2$   
and  $R^3$  are independently selected from  $C_{1-6}$  alkyl  
or  $C_{1-6}$  alkyloxy.

10

6. A pharmaceutical composition comprising the  
compound of claim 1.

15

7. A method of antagonizing a CRF receptor in a mammal  
comprising contacting the receptor with a compound  
of the formula:



(1)

- and isomers thereof, stereoisomeric forms thereof, or  
20 mixtures of stereoisomeric forms thereof, and  
pharmaceutically acceptable salt or pro-drug forms  
thereof, wherein:

X is O or S;

25

A = N or  $CR^9$ ;

- Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R<sup>4</sup> groups and each Ar is attached via an unsaturated carbon atom;
- 10 R<sup>1</sup> is independently selected at each occurrence from H, C<sub>1</sub>-C<sub>4</sub>†alkyl, C<sub>2</sub>-C<sub>4</sub>†alkenyl, C<sub>2</sub>-C<sub>4</sub>†alkynyl, halo, CN, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, C<sub>1</sub>-C<sub>12</sub> hydroxyalkyl, C<sub>2</sub>-C<sub>12</sub> alkoxyalkyl, C<sub>2</sub>-C<sub>10</sub> cyanoalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, NR<sup>9</sup>R<sup>10</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl-NR<sup>9</sup>R<sup>10</sup>, NR<sup>9</sup>COR<sup>10</sup>, OR<sup>11</sup>, SH or S(O)<sub>n</sub>R<sup>12</sup>;
- 15 R<sup>2</sup> is selected from:  
 -H, aryl, heteroaryl and heterocyclyl,  
 or  
 20 -C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-C<sub>8</sub>†cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>1-6</sub> alkyloxy C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>,  
 30 aryl, heteroaryl and heterocyclyl;
- R<sup>3</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†alkenyl, C<sub>3</sub>-C<sub>6</sub>†alkynyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each
- 35

occurrence from C<sub>1</sub>-C<sub>6</sub>+alkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>+haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and heterocyclyl;

R<sup>4</sup> is independently selected at each occurrence from: C<sub>1</sub>-C<sub>10</sub>+alkyl, C<sub>2</sub>-C<sub>10</sub>+alkenyl, C<sub>2</sub>-C<sub>10</sub>+alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-C<sub>12</sub>+cycloalkylalkyl, NO<sub>2</sub>, halo, CN, C<sub>1</sub>-C<sub>4</sub>+haloalkyl, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>, COR<sup>7</sup>, OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, CO(NOR<sup>9</sup>)R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, or S(O)<sub>n</sub>R<sup>7</sup>, where each such C<sub>1</sub>-C<sub>10</sub>+alkyl, C<sub>2</sub>-C<sub>10</sub>+alkenyl, C<sub>2</sub>-C<sub>10</sub>+alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and C<sub>4</sub>-C<sub>12</sub>+cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>4</sub> alkyl, NO<sub>2</sub>, halo, CN, NR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>COR<sup>7</sup>, NR<sup>6</sup>CO<sub>2</sub>R<sup>7</sup>, COR<sup>7</sup> OR<sup>7</sup>, CONR<sup>6</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CO(NOR<sup>9</sup>)R<sup>7</sup>, or S(O)<sub>n</sub>R<sup>7</sup>;

R<sup>6</sup> and R<sup>7</sup> are independently selected at each occurrence from:  
 -H,  
 -C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>10</sub> haloalkyl with 1-10 halogens, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, C<sub>4</sub>-C<sub>12</sub>+cycloalkylalkyl, C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, or C<sub>6</sub>-C<sub>14</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>+alkyl, C<sub>3</sub>-C<sub>6</sub>+cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>+haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl,  
heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heterocyclyl or  
heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl);

- 5 alternatively, NR<sup>6</sup>R<sup>7</sup> is piperidine, pyrrolidine,  
piperazine, N-methylpiperazine, morpholine or  
thiomorpholine, each optionally substituted with 1-3 C<sub>1</sub>-  
C<sub>4</sub> alkyl groups;
- 10 R<sup>8</sup> is independently selected at each occurrence from H or  
C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted by halogen, C<sub>1</sub>-  
C<sub>4</sub> alkoxy or C<sub>1</sub>-C<sub>4</sub> halo-alkoxy (1 to 4 halogens);
- R<sup>9</sup> and R<sup>10</sup> are independently selected at each occurrence  
15 from H, C<sub>1</sub>-C<sub>4</sub> alkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- R<sup>11</sup> is selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, or  
C<sub>3</sub>-C<sub>6</sub> cycloalkyl;
- 20 R<sup>12</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> haloalkyl;
- R<sup>13</sup> is selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub>  
alkoxyalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>4</sub>-  
C<sub>12</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-,  
25 heteroaryl or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl)-;
- R<sup>15</sup> and R<sup>16</sup> are independently selected at each occurrence  
from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>16</sub>  
cycloalkylalkyl, except that for S(O)<sub>n</sub>R<sup>15</sup>, R<sup>15</sup>  
30 cannot be H;
- aryl is phenyl or naphthyl, each optionally substituted  
with 1 to 5 substituents independently selected at  
each occurrence from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
35 halo, C<sub>1</sub>-C<sub>4</sub> haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>15</sup>,

COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>,  
NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>16</sup>R<sup>15</sup>, and CONR<sup>16</sup>R<sup>15</sup>;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl,  
5       pyranyl, quinolinyl, isoquinolinyl, thienyl,  
imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,  
benzofuranyl, benzothienyl, benzothiazolyl,  
isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or  
2,3-dihydrobenzofuranyl, each being optionally  
10       substituted with 1 to 5 substituents independently  
selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-  
C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>,  
SH, S(O)<sub>n</sub>R<sup>15</sup>, -COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>,  
N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>16</sup>R<sup>15</sup>, and  
15       CONR<sup>16</sup>R<sup>15</sup>;

heterocyclyl is saturated or partially saturated  
heteroaryl, optionally substituted with 1 to 5  
substituents independently selected at each  
20       occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl,  
halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>15</sup>,  
COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>15</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>,  
NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, and CONR<sup>16</sup>R<sup>15</sup>;

25       n is independently at each occurrence 0, 1 or 2.

8.       The method according to claim 7 wherein Ar is  
phenyl or pyridyl, each optionally substituted with  
1 to 4 R<sup>4</sup> substituents.

30

9.       The method according to claim 7 wherein Ar is  
phenyl wherein the phenyl is optionally substituted  
with 1 to 3 R<sup>4</sup> substituents.

10. The method according to claim 7 wherein R<sup>2</sup> is:
- C<sub>1</sub>-C<sub>10</sub>†alkyl, C<sub>2</sub>-C<sub>10</sub>†alkenyl, C<sub>2</sub>-C<sub>10</sub>†alkynyl, C<sub>3</sub>-C<sub>8</sub>†cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, C<sub>4</sub>-C<sub>12</sub>†cycloalkylalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C<sub>1</sub>-C<sub>6</sub>†alkyl, C<sub>3</sub>-C<sub>6</sub>†cycloalkyl, halo, C<sub>1</sub>-C<sub>4</sub>†haloalkyl, cyano, OR<sup>15</sup>, SH, S(O)<sub>n</sub>R<sup>13</sup>, COR<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, OC(O)R<sup>13</sup>, NR<sup>8</sup>COR<sup>15</sup>, N(COR<sup>15</sup>)<sub>2</sub>, NR<sup>8</sup>CONR<sup>16</sup>R<sup>15</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>13</sup>, NR<sup>16</sup>R<sup>15</sup>, CONR<sup>16</sup>R<sup>15</sup>, aryl, heteroaryl and heterocyclyl.
11. The method according to claim 7 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkyloxy.
12. The method of claim 7 for treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/31325

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07D 471/02, 487/02; A61K 31/4188; A61P 25/00

US CL : 544/236; 546/118; 514/248, 303

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/236; 546/118; 514/248, 303

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS Online**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	WO 00/01697 A1 (DU PONT PHARMACEUTICALS COMPANY) 13 January 2000 (13.02.00), see entire document.	1-12

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

Date of mailing of the international search report

**19 APR 2000**

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20231

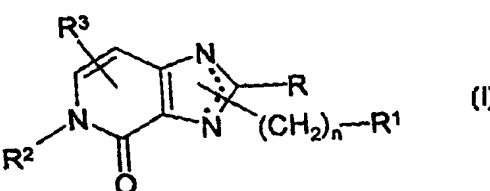
Facsimile No. (703)305-3230

Authorized officer

Brenda Coleman

Telephone No. 703-308-1235


 INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
 INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

<b>(51) Internationale Patentklassifikation <sup>7</sup> :</b> <b>C07D 471/04, A61K 31/437, A61P 9/10 //</b> <b>(C07D 471/04, 235:00, 221:00)</b>	<b>A3</b>	<b>(11) Internationale Veröffentlichungsnummer: WO 00/40583</b>  <b>(43) Internationales Veröffentlichungsdatum:</b> 13. Juli 2000 (13.07.00)
<b>(21) Internationales Aktenzeichen:</b> PCT/EP99/10236  <b>(22) Internationales Anmeldedatum:</b> 21. Dezember 1999 (21.12.99)  <b>(30) Prioritätsdaten:</b> 199 00 471.4      8. Januar 1999 (08.01.99)      DE  <b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b> MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE).  <b>(72) Erfinder; und</b> <b>(75) Erfinder/Anmelder (nur für US):</b> MEDERSKI, Werner [DE/DE]; Am Ohlenberg 29, D-64390 Erzhausen (DE). JURASZYK, Horst [DE/DE]; Kleiner Ring 14, D-64342 Seeheim (DE). WURZIGER, Hanns [DE/DE]; Greinstrasse 7b, D-64291 Darmstadt (DE). TSAKLAKIDIS, Christos [GR/DE]; Rosenbrunnenstrasse 25, D-69469 Weinheim (DE). DORSCH, Dieter [DE/DE]; Königsberger Strasse 17a, D-64372 Ober-Ramstadt (DE). BERNOTAT-DANIELOWSKI, Sabine [DE/DE]; Liebigstrasse 5, D-61231 Bad Neuheim (DE). MELZER, Guido [AT/DE]; Mörikestrasse 6, D-65719 Hofheim (DE). ANZALI, Soheila [IR/DE]; Am Alten Berg 13, D-64342 Seeheim (DE).	<b>(74) Gemeinsamer Vertreter:</b> MERCK PATENT GMBH; D-64271 Darmstadt (DE).  <b>(81) Bestimmungsstaaten:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht.</i>  <b>(88) Veröffentlichungsdatum des internationalen Recherchenberichts:</b> 21. September 2000 (21.09.00)	
<b>(54) Title:</b> IMIDAZO[4,5-C]-PYRIDINE-4-ON-DERIVATIVES  <b>(54) Bezeichnung:</b> IMIDAZO[4,5-C]-PYRIDIN-4-ON-DERIVATE  <div style="text-align: center;">  </div> <b>(57) Abstract</b> <p>The invention relates to novel compounds of formula (I) wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and n have the meaning given in Claim 1. Said compounds are inhibitors of the coagulation factor Xa and can be used for the prophylaxis and/or therapy of thrombo-embolic diseases.</p> <b>(57) Zusammenfassung</b> <p>Neue Verbindungen der Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und n die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.</p>		

### LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
AM	Armenien	FI	Finnland	LT	Litauen	SK	Slowakei
AT	Österreich	FR	Frankreich	LU	Luxemburg	SN	Senegal
AU	Australien	GA	Gabun	LV	Lettland	SZ	Swasiland
AZ	Aserbaidshan	GB	Vereinigtes Königreich	MC	Monaco	TD	Tschad
BA	Bosnien-Herzegowina	GE	Georgien	MD	Republik Moldau	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagaskar	TJ	Tadschikistan
BE	Belgien	GN	Guinea	MK	Die ehemalige jugoslawische Republik Mazedonien	TM	Turkmenistan
BF	Burkina Faso	GR	Griechenland	ML	Mali	TR	Türkei
BG	Bulgarien	HU	Ungarn	MN	Mongolei	TT	Trinidad und Tobago
BJ	Benin	IE	Irland	MR	Mauretanien	UA	Ukraine
BR	Brasilien	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Island	MX	Mexiko	US	Vereinigte Staaten von Amerika
CA	Kanada	IT	Italien	NE	Niger	UZ	Usbekistan
CF	Zentralafrikanische Republik	JP	Japan	NL	Niederlande	VN	Vietnam
CG	Kongo	KE	Kenia	NO	Norwegen	YU	Jugoslawien
CH	Schweiz	KG	Kirgisistan	NZ	Neuseeland	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Demokratische Volksrepublik Korea	PL	Polen		
CM	Kamerun	KR	Republik Korea	PT	Portugal		
CN	China	KZ	Kasachstan	RO	Rumänien		
CU	Kuba	LC	St. Lucia	RU	Russische Föderation		
CZ	Tschechische Republik	LI	Liechtenstein	SD	Sudan		
DE	Deutschland	LK	Sri Lanka	SE	Schweden		
DK	Dänemark	LR	Liberia	SG	Singapur		
EE	Estland						

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/10236

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P9/10 //(C07D471/04,235:00,  
221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 548 934 A (MITSUBISHI CHEM IND) 30 June 1993 (1993-06-30) page 46, line 57 -page 47, line 1; claim 1 -----	1,5
P,A	WO 99 27930 A (MERCK & CO INC (US)) 10 June 1999 (1999-06-10) claims 1,6 -----	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

21 June 2000

Date of mailing of the international search report

30/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 99/10236

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0548934 A	30-06-1993	CA 2085963 A	26-06-1993
		JP 6220044 A	09-08-1994
		US 5401756 A	28-03-1995
		US 5304556 A	19-04-1994
WO 9927930 A	10-06-1999	AU 1539599 A	16-06-1999
		US 6004976 A	21-12-1999

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 99/10236

## A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 7 C07D471/04 A61K31/437 A61P9/10 //(C07D471/04,235:00, 221:00)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

## B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

EPO-Internal, WPI Data, CHEM ABS Data

## C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie <sup>o</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 548 934 A (MITSUBISHI CHEM IND) 30. Juni 1993 (1993-06-30) Seite 46, Zeile 57 -Seite 47, Zeile 1; Anspruch 1	1,5
P,A	WO 99 27930 A (MERCK & CO INC (US)) 10. Juni 1999 (1999-06-10) Ansprüche 1,6	1,5

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

<sup>o</sup> Besondere Kategorien von angegebenen Veröffentlichungen :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

21. Juni 2000

Absendedatum des internationalen Recherchenberichts

30/06/2000

Name und Postanschrift der Internationalen Recherchenbehörde  
Europäisches Patentamt, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Alfaro Faus, I

# INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 99/10236

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP 0548934	A	30-06-1993	CA	2085963 A	26-06-1993
			JP	6220044 A	09-08-1994
			US	5401756 A	28-03-1995
			US	5304556 A	19-04-1994
-----					
WO 9927930	A	10-06-1999	AU	1539599 A	16-06-1999
			US	6004976 A	21-12-1999
-----					



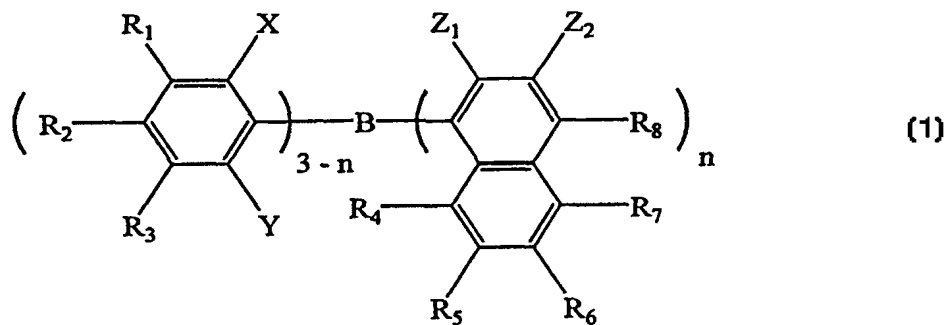
PCT

特許協力条約に基づいて公開された国際出願

(51) 国際特許分類7 C07F 5/02, C09K 11/06, H05B 33/14, 33/22	A1	(11) 国際公開番号 WO00/40586	(43) 国際公開日 2000年7月13日(13.07.00)
(21) 国際出願番号 PCT/JP99/07219		中野隆治(NAKANO, Takaharu)[JP/JP] 〒239-0833 神奈川県横須賀市ハイランド3丁目37番1号 Kanagawa, (JP)	
(22) 国際出願日 1999年12月22日(22.12.99)		小池俊弘(KOIKE, Toshihiro)[JP/JP] 〒236-0024 神奈川県横浜市金沢区乙舩町10番3号 Kanagawa, (JP)	
(30) 優先権データ 特願平11/2786 1999年1月8日(08.01.99)	JP	古川顕治(FURUKAWA, Kenji)[JP/JP] 〒239-0831 神奈川県横須賀市久里浜一丁目16番7号 Kanagawa, (JP)	
(71) 出願人 (米国を除くすべての指定国について) チッソ株式会社(CHISSO CORPORATION)[JP/JP] 〒530-0005 大阪府大阪市北区中之島三丁目6番32号 Osaka, (JP)		(81) 指定国 CA, JP, KR, US, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)	
(72) 発明者 ; および		添付公開書類 国際調査報告書	
(75) 発明者 / 出願人 (米国についてののみ) 玉尾皓平(TAMAO, Kouhei)[JP/JP] 〒606-8301 京都府京都市左京区吉田泉殿町44番地14 Kyoto, (JP)			
山口茂弘(YAMAGUCHI, Shigehiro)[JP/JP] 〒611-0011 京都府宇治市五ヶ庄京大職員宿舎744 Kyoto, (JP)			
内田 学(UCHIDA, Manabu)[JP/JP] 泉澤勇昇(IZUMIZAWA, Takenori)[JP/JP] 〒236-0024 神奈川県横浜市金沢区乙舩町10番2号 Kanagawa, (JP)			

(54)Title: BORANE DERIVATIVES AND ORGANIC ELECTROLUMINESCENTS

(54)発明の名称 ボラン誘導体および有機電界発光素子



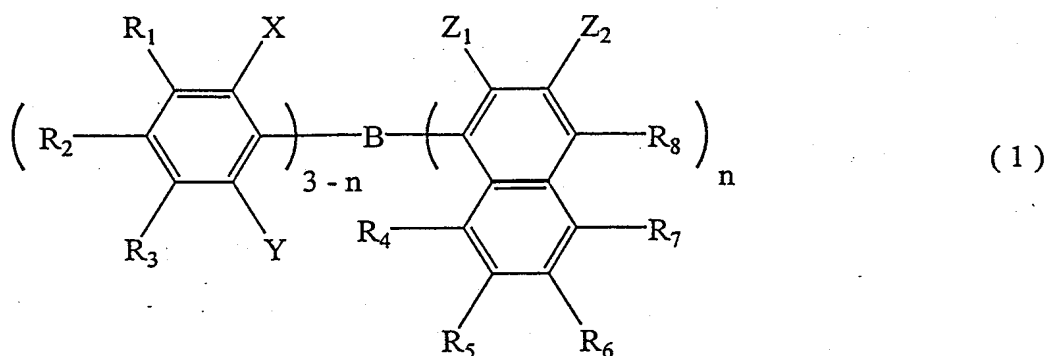
(57) Abstract

Borane derivatives represented by general formula (1) and organic electroluminescents, (wherein R<sub>1</sub> to R<sub>8</sub> and Z<sub>2</sub> are each independently hydrogen, saturated or unsaturated hydrocarbyl, an aromatic group, a heterocyclic group, substituted amino, substituted boryl, alkoxy or aryloxy; X, Y and Z<sub>1</sub> are each independently saturated or unsaturated hydrocarbyl, an aromatic group, a heterocyclic group, substituted amino, alkoxy or aryloxy; or alternatively Z<sub>1</sub> and Z<sub>2</sub> may be united to form a fused ring; and n is an integer of 1 to 3, with the provisos that Z<sub>1</sub>s may be different from each other when n is 2 or above and that cases where n is 1; X, Y and R<sub>2</sub> are each methyl; and R<sub>8</sub> is hydrogen or substituted boryl and those where n is 3; and Z<sub>1</sub> is methyl are excepted). The borane derivatives are suitable for luminescent materials by virtue of their high luminous efficiencies in solid states, and useful for electrophotography and as photoelectronic functional materials including nonlinear optical materials and conductive materials, and the use of the derivatives brings about organic EL devices characterized by low power consumption and high efficiency.



## (57)要約

本発明は、式（１）で表されるボラン誘導体および有機電界発光素子に関する。



（式中、 $R_1 \sim R_8$ および $Z_2$ は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、 $X$ 、 $Y$ および $Z_1$ は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、 $Z_1$ と $Z_2$ の置換基は相互に結合して縮合環を形成してもよく、 $n$ は1～3の整数を示し、 $n$ が2以上の場合、 $Z_1$ は異なってもよい。但し、 $n$ が1、 $X$ 、 $Y$ および $R_2$ がメチル基であって、 $R_8$ が水素原子または置換ボリル基の場合、および $n$ が3で $Z_1$ がメチル基の場合を含まない。）

本発明のボラン誘導体は、固体状態での発光効率が高いので発光材料として好適であり、電子写真、非線形光学材料および導電性材料などの光電子機能材料としても有用である。このボラン誘導体を用いることによって、低消費電力で高効率の有機EL素子を提供することができる。

PCTに基づいて公開される国際出願のパムフレット第一頁に掲載されたPCT加盟国を同定するために使用されるコード(参考情報)

AE アラブ首長国連邦	DM ドミニカ	KZ カザフスタン	RU ロシア
AG アンティグア・バーブーダ	DZ アルジェリア	LC セントルシア	SD スーダン
AL アルバニア	EE エストニア	LI リヒテンシュタイン	SE スウェーデン
AM アルメニア	ES スペイン	LK スリ・ランカ	SG シンガポール
AT オーストリア	FI フィンランド	LR リベリア	SI スロヴェニア
AU オーストラリア	FR フランス	LS レソト	SK スロヴァキア
AZ アゼルバイジャン	GA ガボン	LT リトアニア	SL シェラ・レオネ
BA ボスニア・ヘルツェゴビナ	GB 英国	LU ルクセンブルグ	SN セネガル
BB バルバドス	GD グレナダ	LV ラトヴィア	SZ スワジランド
BE ベルギー	GE グルジア	MA モロッコ	TD チャード
BF ブルキナ・ファソ	GH ガーナ	MC モナコ	TG トーゴ
BG ブルガリア	GM ガンビア	MD モルドヴァ	TJ タジキスタン
BH バハマ	GN ギニア	MG マダガスカル	TM トルクメニスタン
BR ブラジル	GR ギリシャ	MK マケドニア旧ユーゴスラヴィア	TR トルコ
BY ベラルーシ	GW ギニア・ビサオ	共和国	TT トリニダード・トバゴ
CA カナダ	HR クロアチア	ML マリ	TZ タンザニア
CF 中央アフリカ	HU ハンガリー	MN モンゴル	UA ウクライナ
CG コンゴ	ID インドネシア	MR モーリタニア	UG ウガンダ
CH スイス	IE アイルランド	MW マラウイ	US 米国
CI コートジボアール	IL イスラエル	MX メキシコ	UZ ウズベキスタン
CN 中国	IN インド	MZ モザンビーク	VN ヴェトナム
CU キューバ	IS アイスランド	NE ニジェール	YU ユーゴスラヴィア
CR コスタ・リカ	IT イタリア	NL オランダ	ZA 南アフリカ共和国
CY キプロス	JP 日本	NO ノールウェー	ZW ジンバブエ
CZ チェッコ	KE ケニア	NZ ニュー・ジーランド	
DE ドイツ	KG キルギスタン	PL ポーランド	
DK デンマーク	KP 北朝鮮	PT ポルトガル	
	KR 韓国	RO ルーマニア	

## 明 細 書

ボラン誘導体および有機電界発光素子

5

技術分野

本発明は、新規なボラン誘導体、ボラン誘導体を用いた各種材料および有機電  
10 界発光素子（以下、有機EL素子という）に関する。さらに詳しくは、新規な構  
造を有するボラン誘導体、電子機能性材料、光機能性材料などの用途に有用な構  
造を有するボラン誘導体を用いた各種材料および有機EL素子に関する。

背景技術

$\pi$  電子系有機化合物を光機能材料や電子機能材料に応用しようとする試みが多  
15 くの研究機関で行われており、その内容は多種多彩である。

中でも、ボロン原子を分子内に含むボラン化合物は、ボロン原子の空の p 軌道  
の存在によって、特異な光学、電子物性が発現されると予想されている。しかし  
ながら、一般にボラン化合物は、空気や水に対して不安定であるという欠点を有  
しているため、材料としての使用には不向きであった。

20 この様な問題に対して、最近、ボラン化合物を嵩高い構造にすると、つまりボ  
ロン原子のまわりに嵩高い置換基を導入してボロン原子を覆い、ボロン原子を外  
に出さないようにすると、空気や水に対して安定になるという報告がされたこと  
もあり、そのような構造を有するボラン化合物が非線形光学材料や有機EL素子  
の材料等に応用できる可能性が広がった。

25 空気中で安定であるボラン化合物の例が、J. Chem. Soc. Chem. Commun., 1998, 963  
．（以下、文献 1 という）、J. Am. Chem. Soc., 120, 10776(1998)（以下、文献 2 と  
いう）およびJ. Am. Chem. Soc., 120, 5112(1998)（以下、文献 3 という）に報告さ  
れ、ボラン化合物の非線形光学材料への応用例が、Appl. Organomet. Chem., 10, 30  
5(1996)（以下、文献 4 という）に報告され、ボラン化合物の有機EL素子への

応用例が、J. Am. Chem. Soc., 120, 9714 (1998) (以下、文献 5 という) に報告されている。

しかし、文献 2 および文献 3 には、蛍光の極大波長が記載されているが、溶液状態での発光特性に限定されており、実際に使用する固体状態での発光特性に関する記載が全くない。また、その構造もポリマーに限定されており、低分子化合物

物に関しては何も記載されていない。

文献 4 にも、溶液状態での蛍光物性は記載されているが、固体状態での発光性に関する記載が無く、また、発光材料への応用に関しても記載がない。

この様に、嵩高い構造を有するボラン化合物を実質的な用途に用いるには、充分な研究が行われていると言えないのが現状である。特に、有機 EL 素子への材料に応用することが熱望されており、この種の研究がさかんに行われているが、いまだ満足ゆく結果は得られていなかった。

有機 EL 素子は、基本的には 2 つの電極に電荷輸送材料または／および発光材料となる有機化合物を挟んだ構造からなる。低消費電力で高効率な有機 EL 素子であることが望ましく、そのためには発光効率の高い発光材料となる有機化合物を用いる必要がある。

ところが、文献 5 には、5, 5' - ビス (ジメシチルボリル) - 2, 2' - (ビチオフェン) や 5, 5'' - ビス (ジメシチルボリル) - 2, 2' : 5', 2'' - (ターチオフェン) のようなボラン化合物を有機 EL 素子の電子輸送材料 (電荷輸送材料) に用いることが記載されているものの、該ボラン化合物の発光特性および該ボラン化合物の発光材料としての適性に関しては全く触れられていない。わずかに、ボラン化合物を用いない素子に比べ該ボラン化合物を用いた素子は、同輝度における電流密度が低いので、発光効率が向上していることを意味するという報告がなされているに過ぎない。

また、特開平 7 - 1 0 2 2 5 1 号公報においても、ホウ素化合物を有機 EL 素子に利用した例が示されている。しかし、ここで用いられているホウ素化合物は、駆動電圧が高く、発光輝度も低いものであった。

この様に、ボラン化合物の発光特性に関する文献等が少ないため、有機 EL 素子の材料としてこれまでに知られているボラン化合物では、低消費電力で高効率

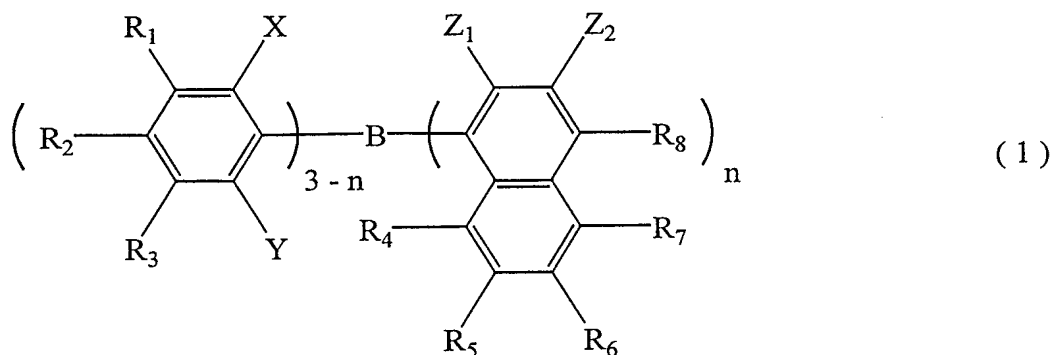
な有機EL素子を得ることができなかった。そのため、有機EL素子の材料として有効に働くボラン化合物の構造特定が望まれていた。

### 発明の開示

- 5 本発明者等は、新規なボラン誘導体、ボラン誘導体を用いた各種材料および有機EL素子を提供するという課題を解決すべく鋭意検討を進めた結果、特定構造を有するボラン誘導体および特定構造を有するボラン誘導体を材料に用いること、特に有機EL素子に用いることにより、上記課題を解決し得ることを知り本発明を完成した。

- 10 以下、本発明につき詳細に説明する。

本発明のボラン誘導体は、下記の式(1)で表される新規な化合物である。本発明のボラン誘導体は、発光材料および電荷輸送材料ばかりでなく、ボラン原子に由来する電子的性質を利用して、電子機能性材料および光機能性材料などへの広範な応用が期待できるものである。



15

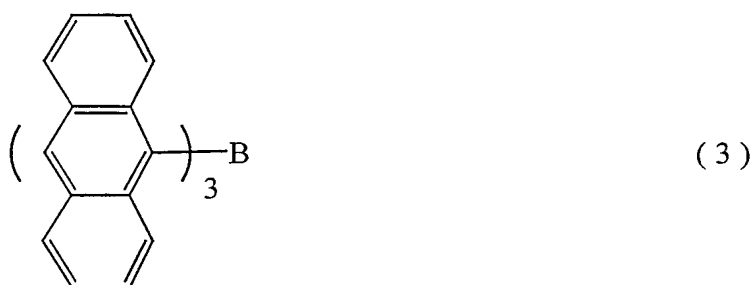
- (式中、 $R_1 \sim R_8$ および $Z_2$ は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、 $X$ 、 $Y$ および $Z_1$ は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、 $Z_1$ と $Z_2$ の置換基は相互に結合して縮合環を形成してもよく、 $n$ は1～3の整数を示し、 $n$ が2以上の場合、 $Z_1$ は異なってもよい。但し、 $n$ が1、 $X$ 、 $Y$ および $R_2$ がメチル基であって、 $R_8$
- 20

が水素原子または置換ボリル基の場合、および  $n$  が 3 で  $Z_1$  がメチル基の場合を含まない。)

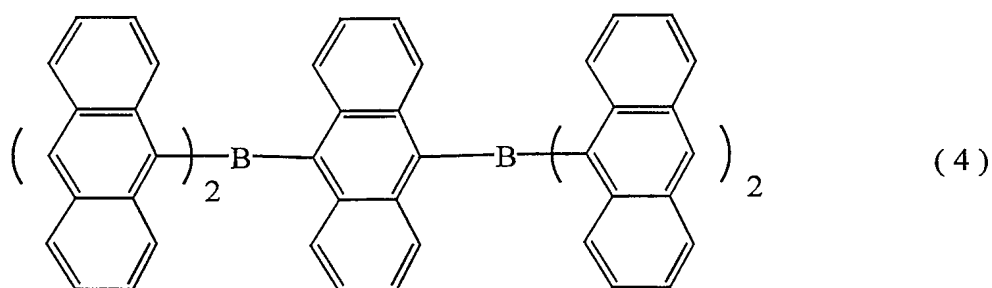
そして、この式 (1) で表されるボラン誘導体の中でも、ボロン原子に対して少なくとも 1 個の置換もしくは無置換の 9-アンスリル基が結合しているものが

5 好ましい。

本発明のボラン誘導体の具体的例として、下記の式 (3) ~ (9) で表される化合物を挙げることができる。

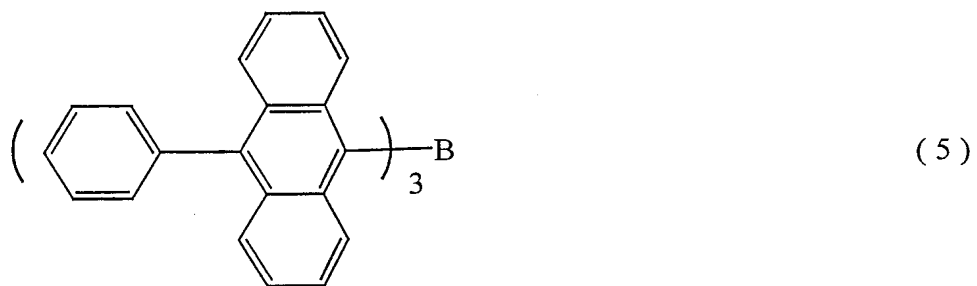


10 式 (3) の化合物は、上記の式 (1) において、 $n$  が 3、 $R_4 \sim R_8$  が水素原子、 $Z_1$  と  $Z_2$  とがベンゾ縮合したボラン誘導体である。



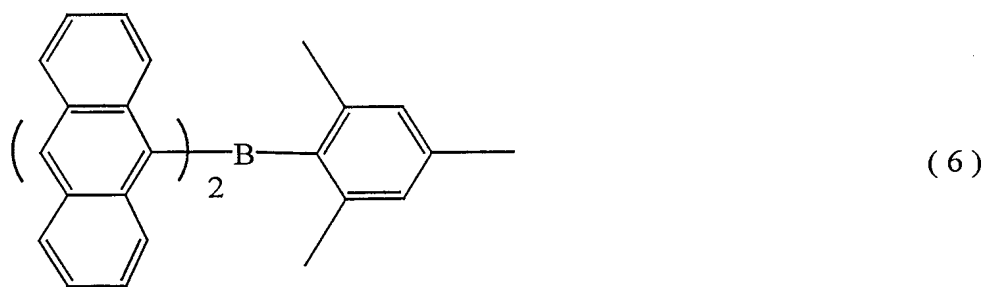
式 (4) の化合物は、上記の式 (1) において、 $n$  が 3、 $R_4 \sim R_7$  が水素原

15 子、 $R_8$  の 1 つがジアンスリルボリル基、 $R_8$  の残り 2 つが水素原子、 $Z_1$  と  $Z_2$  とがベンゾ縮合したボラン誘導体である。



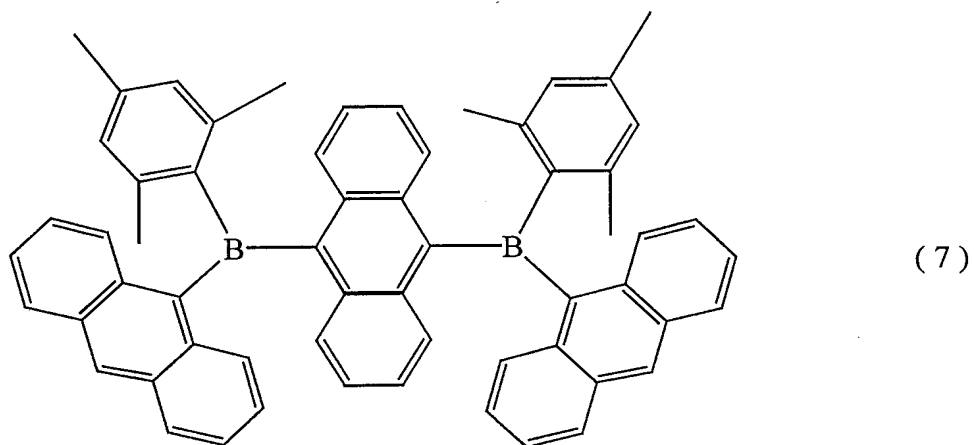
式(5)の化合物は、上記の式(1)において、 $R_4 \sim R_7$ が水素原子、 $R_8$ がフェニル基、 $n$ が3、 $Z_1$ と $Z_2$ とがベンゾ縮合したボラン誘導体である。

5



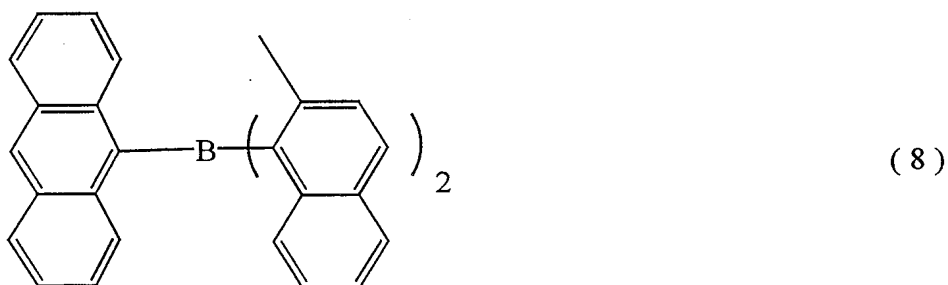
式(6)の化合物は、上記の式(1)において、 $n$ が2、 $R_1$ および $R_3 \sim R_8$ が水素原子、 $R_2$ 、 $X$ および $Y$ がメチル基、 $Z_1$ と $Z_2$ とがベンゾ縮合したボラン誘導体である。

10



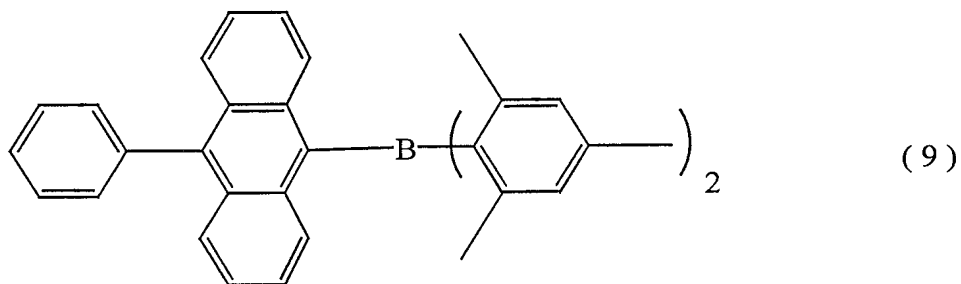
式(7)の化合物は、上記の式(1)において、 $n$ が2、 $R_1$  および  $R_3 \sim R_7$  が水素原子、 $R_2$ 、 $X$ および $Y$ がメチル基、 $R_8$  の1つがアンスリルメシチルボリル基、 $R_8$  の残り1つが水素原子、 $Z_1$  と  $Z_2$  とがベンゾ縮合したボラン誘導体である。

5



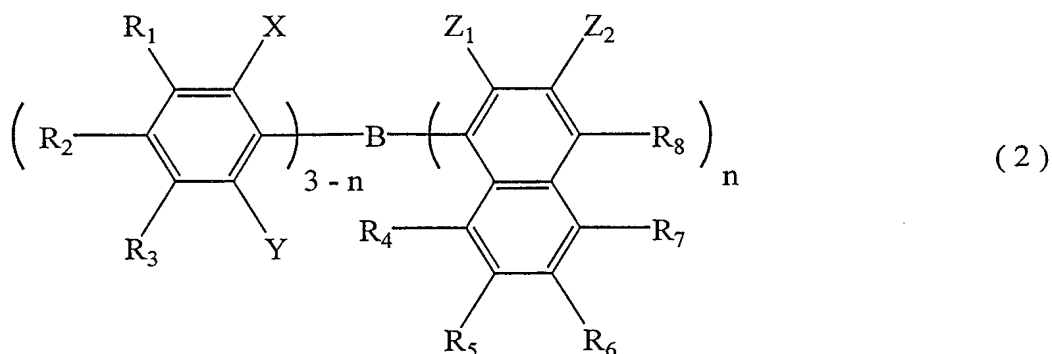
式(8)の化合物は、上記の式(1)において、 $n$ が3、 $R_4 \sim R_8$  が水素原子、 $Z_1$  と  $Z_2$  が1カ所でベンゾ縮合し、縮合していない残り2つの  $Z_1$  がメチル基、縮合していない残り2つの  $Z_2$  が水素原子のボラン誘導体である。

10



式(9)の化合物は、上記の式(1)において、 $n$ が1、 $R_1$  および  $R_3 \sim R_7$  が水素原子、 $R_2$ 、 $X$ および $Y$ がメチル基、 $R_8$  がフェニル基、 $Z_1$  と  $Z_2$  とがベンゾ縮合したボラン誘導体である。

15 本発明の各種材料、すなわち発光材料、電荷輸送材料および有機EL素子関連材料(発光層、電荷輸送層)に用いられるボラン誘導体は、下記の式(2)で表される。



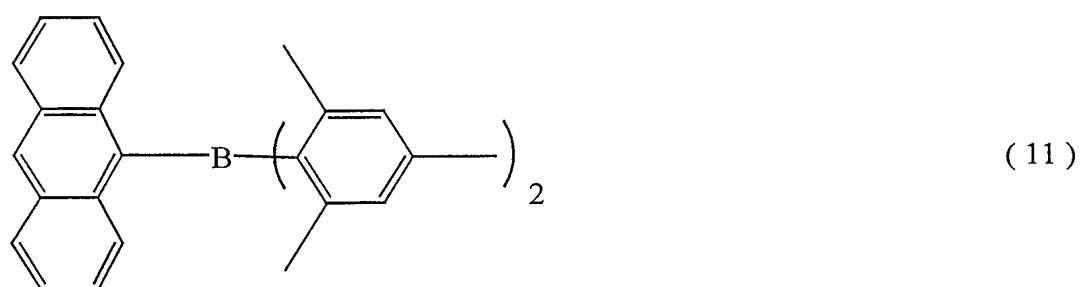
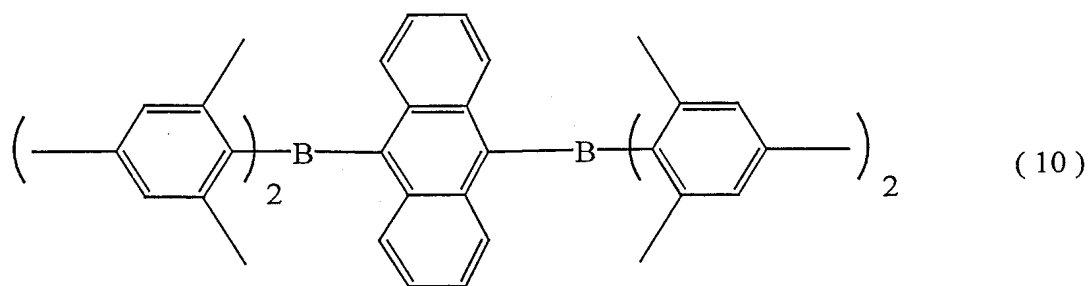
(式中、 $R_1 \sim R_8$ および $Z_2$ は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、 $X$ 、 $Y$ および $Z_1$ は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、 $Z_1$ と $Z_2$ の置換基は相互に結合して縮合環を形成してもよく、 $n$ は1～3の整数を示し、 $n$ が2以上の場合、 $Z_1$ は異なってもよい。)

- 10 該ボラン誘導体は、空気中においても安定で、材料としての十分な耐久性および性能を持たせるため、嵩高い構造であることが好ましく、アントラセン環および／またはナフタレン環を有していることが望ましい。

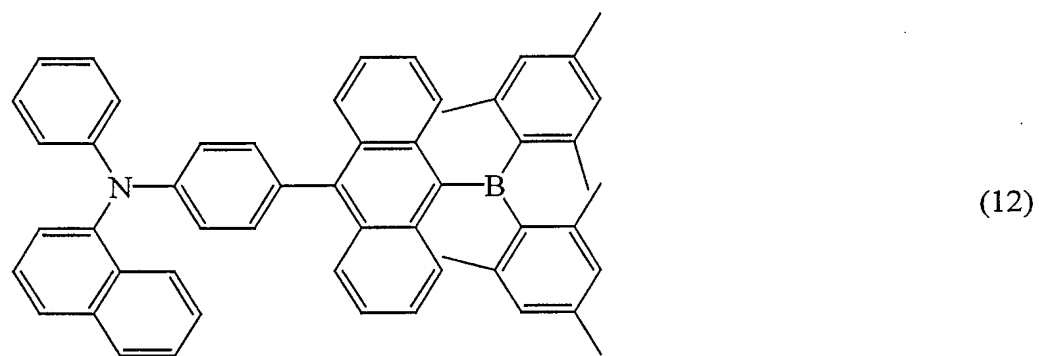
従って、本発明の発光材料、電荷輸送材料および有機EL素子には、上記の式(2)で表されるボラン誘導体の中でも、ボロン原子に対して少なくとも1個の置換もしくは無置換の9-アンスリル基が結合しているものが好ましい。

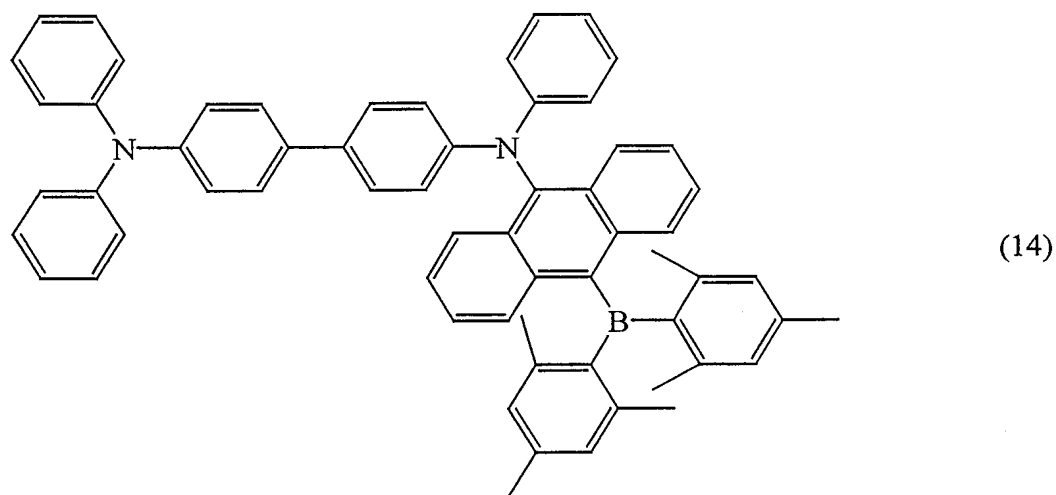
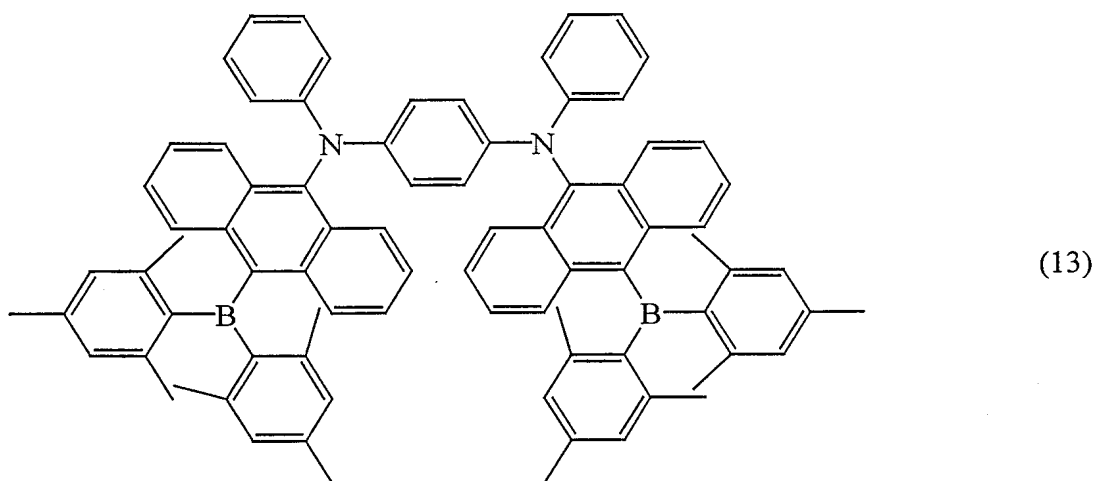
このようなボラン誘導体の具体例として、前記の式(3)～(9)で表される化合物および下記の式(10)～(14)で表される化合物などを挙げることができる。





5

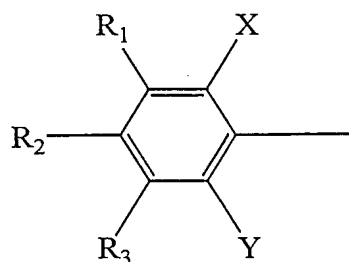




本発明のボラン誘導体および本発明の各種材料に用いられるボラン誘導体（以下、便宜的に本発明のボラン誘導体と略す）は、以下に示す製造法に代表される公知の手法により合成することができる。すなわち、一般式（15）で表される化合物に塩基を反応させ、続いてボラン化合物を反応させることにより合成できる。

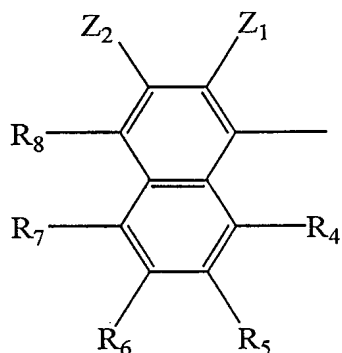


（式中、Ar は下記の式（16）または式（17）を示し、Wはハロゲン原子を示す。）



(16)

- (式中、R<sub>1</sub>～R<sub>3</sub>は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、XおよびYは、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示す。)



(17)

- 10 (式中、R<sub>4</sub>～R<sub>8</sub>およびZ<sub>2</sub>は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、Z<sub>1</sub>は飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z<sub>1</sub>とZ<sub>2</sub>の置換基は相互に結合して縮合環を形成してもよい。)
- 15 この製造法において用いられる塩基としては、例えば、n-ブチルリチウム、tert-ブチルリチウム、フェニルリチウムなどの有機リチウム試薬、マグネシウム、マグネシウムブロマイドなどのマグネシウム試薬等が挙げられる。また、用いられる溶媒としては、これらの塩基に不活性なものなら特に制限はなく、通常、

ジエチルエーテルあるいはテトラヒドロフラン（以下、THFという）のようなエーテル系もしくはベンゼン、トルエンなどの芳香族系の溶媒が用いられる。さらに、用いられるボラン化合物としては、トリクロロボラン、トリフルオロボランまたはそれらの錯体などのハロゲン化ボラン類、トリメトキシボランまたはトリイソプロポキシボランなどのアルコキシボラン類などが挙げられる。

これらの反応は、不活性ガス中で行うことが好ましく、窒素およびアルゴンガスなどが使われる。反応温度は、特に制限はないが、通常、 $-78^{\circ}\text{C}\sim 120^{\circ}\text{C}$ 程度が好ましい。これらの反応には、特に反応時間に制限はなく、反応が十分に進行している時点で反応を止めればよい。NMRあるいはクロマトグラフィー等の一般的な分析手段により反応を追跡し、最適の時点で反応の終点を決定すればよい。

また、得られた化合物に対して、置換反応を行うことによっても本発明のボラン誘導体を得られる。

置換反応によって付加する置換基としては、メチル基、エチル基、ノルマルプロピル基、イソプロピル基、シクロペンチル基、およびtert-ブチル基などのアルキル基、ビニル基、アリル基、ブテニル基およびスチリル基などのアルケニル基、メトキシ基、エトキシ基、プロポキシ基、フェニルオキシ基などのアルコキシ基もしくはアリールオキシ基、ジメチルアミノ基、ジフェニルアミノ基などのアミノ基、トリメチルシリル基、ジメチル-tert-ブチルシリル基、トリメトキシシリル基およびトリフェニルシリル基などのシリル基、ジアンシリルボリル基、ジメシチルボリル基などのボリル基、フェニル基、ナフチル基、アンシリル基、ビフェニル基、トルイル基、ピレニル基、ペリレニル基、アニシル基、ターフェニル基およびフェナンスレニル基などのアリール基、ヒドロフリル基、ヒドロピレニル基、ジオキサニル基、チエニル基、フリル基、オキサゾリル基、オキサジアゾリル基、チアゾリル基、チアジアゾリル基、アクリジニル基、キノリル基、キノキサロイル基、フェナンスロリル基、ベンゾチエニル基、ベンゾチアゾリル基、インドリル基、シラシクロペンタジエニル基およびピリジル基などのヘテロ環などが挙げられる。

更に、これらの置換基がお互いに任意の場所で結合して環を形成しても良い。

本発明の有機EL素子は、基本的には一対の電極（陽極と陰極）間に、前記の式（２）で表されるボラン誘導体を主成分とするボラン誘導体層を挟持した構造を有するものである。

5 該ボラン誘導体は、発光材料としても電荷輸送材料としても使用可能であるため、発光層および電荷輸送層（正孔注入層、正孔輸送層、電子注入層および電子輸送層）の材料に好適であり、得られた該ボラン誘導体層は、発光層および電荷輸送層として有効に働く。

10 また、該ボラン誘導体層には、該ボラン誘導体以外の正孔注入材料、正孔輸送材料、発光材料、電子注入材料あるいは電子輸送材料などが添加されていても良い。

有機EL素子においては、多くの場合、電荷輸送材料となる電子供与性化合物と電子受容性化合物とが用いられており、これらの混合物を添加したり、これらを積層したりして使用されているが、これらは好ましくない電荷移動錯体又はエキサイプレックスを形成することも知られている。しかし、本発明で用いられる  
15 ボラン誘導体は、ボロン原子に結合している嵩高い基が、ボロン原子を中心としてプロペラ状に配置されているため、電荷移動錯体又はエキサイプレックスを形成しにくい構造となっている。従って、該ボラン誘導体を電子供与性化合物または電子受容性化合物として有機EL素子の材料に使用すると、高効率な素子が得られやすい利点を有している。

20 本発明の有機EL素子には、電極間に該ボラン誘導体層の他に、正孔注入層、正孔輸送層、発光層、電子注入層、電子輸送層および界面層などを任意に設けても何等差し支えない。

本発明の有機EL素子の具体的な構成としては、

構成（１）陽極／ボラン誘導体層／陰極

25 構成（２）陽極／正孔注入層／ボラン誘導体層／陰極

構成（３）陽極／ボラン誘導体層／電子注入層／陰極

構成（４）陽極／正孔注入層／ボラン誘導体層／電子注入層／陰極

構成（５）陽極／正孔注入層／ボラン誘導体層／電子輸送層／界面層／陰極

構成（６）陽極／正孔注入層／正孔輸送層／ボラン誘導体層／電子注入層／陰極

構成（７）陽極／正孔注入層／正孔輸送層／ボラン誘導体層／電子注入層／界面層／陰極

などの積層構造を挙げることができる。

- 5 この場合、正孔注入層、電子注入層、正孔輸送層、電子輸送層および界面層は、必ずしも必要ではないが、これらの層を設けることにより、発光効率を向上させることができる。特に、正孔注入層及び正孔輸送層の導入は、発光効率を大幅に向上させる。

本発明の有機EL素子は、基板に支持されていることが好ましい。

- 10 基板としては、機械的強度、熱安定性および透明性を有するものであればよく、ガラス、透明プラスチックフィルムなどを用いることができる。

- 本発明の有機EL素子の陽極に用いられる陽極物質としては、 $4\text{ e V}$ より大きな仕事関数を有する金属、合金、電気伝導性化合物及びこれらの混合物を用いることができる。具体例として、Auなどの金属、CuI、インジウムチンオキシド（以下、ITOという）、 $\text{SnO}_2$ 、ZnOなどの導電性透明材料が挙げら
- 15 れる。

- また、本発明の有機EL素子の陰極に用いられる陰極物質としては、 $4\text{ e V}$ より小さな仕事関数の金属、合金、電気伝導性化合物、およびこれらの混合物を使用できる。具体例としては、カルシウム、マグネシウム、リチウム、アルミニウム、マグネシウム合金、リチウム合金、アルミニウム合金等があり、混合物とし
- 20 てはアルミニウム／リチウム、マグネシウム／銀、マグネシウム／インジウムなどが挙げられる。

- 本発明では、有機EL素子の発光を効率よく取り出すために、電極の少なくとも一方は光透過率が $10\%$ 以上とすることが望ましい。電極としてのシート抵抗は数百 $\Omega/\text{mm}$ 以下とするのが好ましい。なお、膜厚は電極材料の性質にもよる
- 25 が、通常 $10\text{ nm}\sim 1\text{ }\mu\text{ m}$ 、好ましくは $10\sim 400\text{ nm}$ の範囲で選定される。このような電極は、上述の電極物質（陽極物質と陰極物質）を使用して蒸着やスパッタリングなどの方法により薄膜を形成させることにより作製することができる。

本発明の有機EL素子の必須構成層である発光層には、前記の式（２）で表さ

れるボラン誘導体が用いられていることが望ましいが、該ボラン誘導体以外の発  
光材料が用いられても良い。また、式(2)で表されるボラン誘導体と該ボラン  
誘導体以外の発光材料との混合物を用い、該ボラン誘導体とは異なる波長の光を  
発生させたり、さらに発光効率を向上させることもできる。なお、式(2)で表

5 されるボラン誘導体を2種以上組み合わせて用いることにも、何ら問題はない。

この様な式(2)で表されるボラン誘導体以外の発光材料には、高分子学会編  
高分子機能材料シリーズ”光機能材料”、共立出版(1991)、P236に記載されてい  
るような昼光蛍光材料、蛍光増白剤、レーザー色素、有機シンチレータ、各種の  
蛍光分析試薬などの公知物質を挙げることができる。

10 具体的には、アントラセン、フェナントレン、ピレン、クリセン、ペリレン、  
コロネン、ルブレン、キナクリドンなどの多環縮合化合物、クオーターフェニル  
などのオリゴフェニレン系化合物、1,4-ビス(2-メチルスチリル)ベンゼン、1,4-  
ビス(4-メチルスチリル)ベンゼン、1,4-ビス(4-メチル-5-フェニル-2-オキサゾ  
15 リル)ベンゼン、1,4-ビス(5-フェニル-2-オキサゾリル)ベンゼン、2,5-ビス(5-  
タシャリー-ブチル-2-ベンズオキサゾリル)チオフェン、1,4-ジフェニル-1,3-フ  
タジエン、1,6-ジフェニル-1,3,5-ヘキサトリエン、1,1,4,4-テトラフェニル-1,  
3-ブタジエンなどの液体シンチレーション用シンチレータ、特開昭63-264  
692号公報記載のオキシシン誘導体の金属錯体、クマリン染料、ジシアノメチレ  
ンピラン染料、ジシアノメチレンチオピラン染料、ポリメチン染料、オキシベン  
20 ズアントラセン染料、キサンテン染料、カルボスチリル染料およびペリレン染料  
、独国特許2534713号公報に記載のオキサジン系化合物、第40回応用物理  
学関係連合講演会講演予稿集、1146(1993)に記載のスチルベン誘導体、特開平7  
-278537号公報記載のスピロ化合物および特開平4-363891号公報  
記載のオキサジアゾール系化合物などが好ましい。

25 本発明の有機EL素子の選択的構成層である正孔注入層は、正孔注入材料を用  
いて得ることができるが、この際、一種以上の正孔注入材料を用いて1層の正孔  
注入層を得ても良く、異なる数種の正孔注入材料を用いて複数の正孔注入層を得  
ても良い。

また、本発明の有機EL素子の選択的構成層である正孔輸送層は、正孔輸送材

料を用いて得ることができるが、この際、一種以上の正孔輸送材料を用いて1層の正孔輸送層を得ても良く、異なる数種の正孔輸送材料を用いて複数の正孔輸送層を得ても良い。

該正孔注入材料および該正孔輸送材料には、前記の式(2)で表されるボラン誘導体を用いることができるが、光導電材料において、正孔の電荷輸送材料として従来から慣用されているものや、有機EL素子の正孔注入層および正孔輸送層に使用され得る公知物質の中から任意のものを選択して用いることもできる。

この様な公知物質としては、例えば、カルバゾール誘導体(N-フェニルカルバゾール、ポリビニルカルバゾールなど)、トリアリールアミン誘導体(TPD、芳香族第3級アミンを主鎖あるいは側鎖に持つポリマー、1,1-ビス(4-ジ-p-トリルアミノフェニル)シクロヘキサン、N,N'-ジフェニル-N,N'-ジナフチル-4,4'-ジアミノビフェニル(以下、NPDと略記する)、4,4',4''-トリス{N-(3-メチルフェニル)-N-フェニルアミノ}トリフェニルアミン、ジャーナル・オブ・ザ・ケミカル・ソサイエティー・ケミカル・コミュニケーション第2175ページ1996年に記載されている化合物、特開昭57-144558号公報、特開昭61-62038号公報、特開昭61-124949号公報、特開昭61-134354号公報、特開昭61-134355号公報、特開昭61-112164号公報、特開平4-308688号公報、特開平6-312979号公報、特開平6-267658号公報、特開平7-90256号公報、特開平7-97355号公報、特開平6-1972号公報、特開平7-126226号公報、特開平7-126615号公報、特開平7-331238号公報、特開平8-100172号公報および特開平8-48656号公報に記載されている化合物、アドバンスド・マテリアル第6巻第677ページ1994年に記載されているスターバーストアミン誘導体など)、スチルベン誘導体(日本化学会第72春季年会講演予稿集(II)、1392ページ、2PB098に記載のものなど)、フタロシアニン誘導体(無金属、銅フタロシアニンなど)、ポリシランなどが挙げられる。

本発明の有機EL素子の選択的構成層である電子注入層は、電子注入材料を用いて得ることができるが、この際、一種以上の電子注入材料を用いて1層の電子注入層を得ても良く、異なる数種の電子注入材料を用いて複数の電子注入層を得



ても良い。

また、本発明の有機EL素子の選択的構成層である電子輸送層は、電子輸送材料を用いて得ることができるが、この際、一種以上の電子輸送材料を用いて1層の電子輸送層を得ても良く、異なる数種の電子輸送材料を用いて複数の電子輸送層を得ても良い。

該電子注入材料および該電子輸送材料には、前記の式(2)で表されるボラン誘導体を用いることが望ましいが、光導電材料において、電子伝達化合物として従来から慣用されているもの、有機EL素子の電子注入層および電子輸送層に使用され得る公知物質の中から任意のものを選択して用いることができる。

- 10 この様な公知物質としては、例えば、ジフェニルキノン誘導体(電子写真学会誌、30,3(1991)などに記載のもの)、ペリレン誘導体(J. Apply. Phys., 27, 269(1988)などに記載のもの)や、オキサジアゾール誘導体(前記文献、Jpn. J. Appl. Phys., 27, L713(1988)、アプライド・フィジックス・レター(Appl. Phys. Lett.), 55, 1489(1989)などに記載のもの)、チオフェン誘導体(特開平4-212286号公報などに記載のもの)、トリアゾール誘導体(Jpn. J. Appl. Phys., 32, L917(1993)などに記載のもの)、チアジアゾール誘導体(第43回高分子学会予稿集、(III)P1a007などに記載のもの)、オキシシン誘導体の金属錯体(電子情報通信学会技術研究報告、92(311), 43(1992)などに記載のもの)、キノキサリン誘導体のポリマー(Jpn. J. Appl. Phys., 33, L250(1994)などに記載のもの)、フェナントロリン誘導体(第43回高分子討論会予稿集、14J07などに記載のもの)などを挙げる  
15  
20 ことができる。

本発明の有機EL素子に用いることのできる正孔注入材料、正孔輸送材料、発光材料および電子注入材料などには、好ましくはT<sub>g</sub>が80℃以上のもの、より好ましくはT<sub>g</sub>が100℃以上のものである。

- 25 本発明の有機EL素子の選択的構成層である界面層としては、陰極からの電子の注入を促進させられるものが好ましく、また陰極への正孔の流れ込みを阻止するものが好ましい。これらは、陰極に用いられる材料との相性によって選択され、その具体例としては、フッ化リチウム、フッ化マグネシウム、フッ化カルシウムなどが挙げられる。

本発明の有機EL素子を構成する各層は、各層を構成すべき材料を蒸着法、スピコート法およびキャスト法などの公知の方法で薄膜とすることにより、形成することができる。

5 このようにして形成された各層の膜厚については特に制限はなく、素材の性質に応じて適宜選定することができるが、通常2 nm～5 0 0 0 nmの範囲で選定される。

蒸着法を用いて薄膜化する場合、その蒸着条件は、ボラン誘導体の種類、分子累積膜の目的とする結晶構造及び会合構造などにより異なるが、一般に、ボート加熱温度5 0～4 0 0℃、真空度 $10^{-6} \sim 10^{-3}$  Pa、蒸着速度0. 0 1～5  
10 0 nm/秒、基板温度-1 5 0～+3 0 0℃、膜厚5 nm～5 μmの範囲で適宜選定することが望ましい。

次に、本発明の有機EL素子を作製する方法の一例として、前記構成(1)の陽極/ボラン誘導体層/陰極からなる有機EL素子の作製法について説明する。

適当な基板上に、陽極物質からなる薄膜を、1 μm以下、好ましくは1 0～2  
15 0 0 nmの範囲の膜厚になるように、蒸着法により形成させて陽極を作製した後、この陽極上にボラン誘導体の薄膜を形成させて発光層とし、この発光層の上に陰極物質からなる薄膜を蒸着法により、1 μm以下の膜厚になるよう形成させて陰極とすることにより、目的の有機EL素子が得られる。

なお、上述の有機EL素子の作製においては、作製順序を逆にして、陰極、発  
20 光層、陽極の順に作製することも可能である。

この様にして得られた有機EL素子に直流電圧を印加する場合には、陽極を+、陰極を-の極性として印加すれば良く、電圧2～4 0 V程度を印加すると、透明又は半透明の電極側(陽極又は陰極、及び両方)より発光が観測できる。

また、この有機EL素子は、交流電圧を印加した場合にも発光する。なお、印  
25 加する交流の波形は任意でよい。

#### 発明を実施するための最良の形態

以下に実施例にて本発明を具体的に説明するが、本発明は下記の実施例に限定されるものではない。

<ボラン誘導体の合成例>

(実施例 1) : 前記の式 (4) で表される化合物の合成

アルゴン気流下、9-ブロモアントラセンを 5.14 g 含むエーテル溶液 30 ml に対し、n-ブチルリチウム 1.6 mol/l のヘキサン溶液 13 ml を -78  
5 °C 設定下で加えた後、0 °C まで昇温して 30 分間攪拌し、続いて同温でボロントリフルオライド 4.1 ml を含むエーテル溶液 10 ml に加え、1 時間攪拌して黄色固体の析出物を得た。

その後、上澄みを除去し、乾燥エーテル 30 ml を添加して、1 時間攪拌した後、再度上澄みを除去し、乾燥 THF 30 ml を加えた。

10 更に、9,10-ジリチオアントラセンのエーテル溶液を滴下し、室温で 3 時間攪拌して、析出物をろ過により除去し、ろ液を濃縮し、酢酸エチルを加え、析出物を酢酸エチルから再結晶し、目的の化合物を得た。その収率は 4 % であった。この化合物は、固体状態で赤色の蛍光を発した。

$^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ )  $\delta$  = 6.41 (dd, 4H), 6.77 (t, 8H), 7.06 (t, 8H), 7.77 (d, 8H), 8.35 (s, 4H), 8.59-8.63 (m, 12H).

(実施例 2) : 前記の式 (6) で表される化合物の合成

実施例 1 で用いた 9,10-ジリチオアントラセンをメシチルリチウムに替えた以外は、実施例 1 に準ずる方法で合成した。

20  $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ )  $\delta$  = 2.0 (s, 6H), 2.10 (s, 3H), 6.71 (s, 2H), 6.91 (t, 4H), 6.88-6.94 (m, 4H), 7.06-7.12 (m, 4H), 8.35 (s, 2H), 8.49 (d, 4H).

(実施例 3) : 前記の式 (3) で表される化合物の合成

アルゴン気流下、9-ブロモアントラセンを 5.14 g 含むエーテル溶液 30  
25 ml に対し、n-ブチルリチウム 1.6 mol/l のヘキサン溶液 13 ml を -78 °C 設定下で加えた後、0 °C まで昇温して 30 分間攪拌し、続いて同温でボロントリフルオライド 0.8 ml を含むエーテル溶液 10 ml に加え、12 時間攪拌して、橙色固体の析出物を得た。

析出物をベンゼンから再結晶し、目的の化合物を得た。その収率は 33 % であ

った。

$^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ )  $\delta = 6.83\text{--}6.89$  (m, 6H),  $7.21$  (t, 4H),  $7.95$  (d, 6H),  $8.12$  (d, 6H),  $8.58$  (s, 4H).

## 5 <有機EL素子の製造例およびその特性>

### (実施例4)

25 mm×75 mm×1.1 mmのガラス基板上にITOを蒸着法にて100 nmの厚さに蒸着したもの(東京三容真空(株)製)を透明支持基板とした。この透明支持基板を市販の蒸着装置(真空機工(株)製)の基板ホルダーに固定し

10 N, N'-ジナフチル-N, N'-ジフェニルベンジジン(以下NPDと略記する)をいれた石英るつぼ、前記の式(10)で表される化合物を入れた石英るつぼ、1, 1-ジメチル-2, 5-ビス{2-(2-ピリジル)ピリジル}-3, 4-ジフェニルシラシクロペンタジエン(以下、PYPYという)を入れた石英るつぼ、マグネシウムを入れたグラファイト製のるつぼ、および銀を入れたグラ

15 ファイト製のるつぼを装着した。

真空槽を $1 \times 10^{-3}$  Paまで減圧し、NPD入りのるつぼを加熱して、膜厚50 nmになるようにNPDを蒸着して正孔輸送層を形成し、次いで、前記の式(10)で表される化合物入りのるつぼを加熱して、膜厚15 nmになるように蒸着して発光層を形成し、次いで、PYPY入りのるつぼを加熱して、膜厚35 nm

20 mになるようにPYPYを蒸着して電子輸送層を形成した。蒸着速度は0.1~0.2 nm/秒であった。

その後真空槽を $2 \times 10^{-4}$  Paまで減圧し、グラファイト製のるつぼを加熱して、マグネシウムを1.2~2.4 nm/秒の蒸着速度で、同時に銀を0.1~0.2 nm/秒の蒸着速度で蒸着し、有機層の上に150 nmのマグネシウムと

25 銀の合金電極を形成することにより、有機EL素子を得た。

ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約1 mA/cm<sup>2</sup>の電流が流れ、輝度約100 cd/m<sup>2</sup>、波長515 nmの緑色の発光を得た。

## (比較例 1)

前記の式 (10) で表される化合物をトリス (8-ヒドロキシキノリン) アルミニウムに替えた以外は、実施例 4 に準ずる方法で素子を作成した。

- 5 ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $1 \text{ mA/cm}^2$  の電流が流れ、輝度約  $20 \text{ cd/m}^2$ 、波長  $522 \text{ nm}$  の緑色の発光を得たが、実施例 4 に比べて、発光輝度が約  $1/5$  に低下した。

## (比較例 2)

- 10 前記の式 (10) で表される化合物をトリメシチルボランに替えた以外は、実施例 4 に準ずる方法で素子を作成した。

ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $50 \text{ mA/cm}^2$  の電流が流れ、輝度約  $5 \text{ cd/m}^2$  の紫色の発光を得たが、実施例 4 に比べて、発光輝度及び発光効率が大幅に低下した。

15

## (実施例 5)

実施例 4 で用いた PYPY を使用せずに、式 (10) で表される化合物からなる層の膜厚を  $50 \text{ nm}$  に替えた以外は、実施例 4 に準ずる方法で素子を作成した。

- 20 ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $1 \text{ mA/cm}^2$  の電流が流れ、輝度約  $6 \text{ cd/m}^2$ 、波長  $515 \text{ nm}$  の緑色の発光を得た。

## (実施例 6)

- 25 実施例 4 で用いた式 (10) で表される化合物を、前記の式 (4) で表される化合物に替えた以外は、実施例 4 に準ずる方法で素子を作成した。

ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $1 \text{ mA/cm}^2$  の電流が流れ、輝度約  $6 \text{ cd/m}^2$ 、波長  $616 \text{ nm}$  の赤色の発光を得た。

## (実施例 7)

実施例 4 で用いた式 (10) で表される化合物を、前記の式 (11) で表される化合物に替えた以外は、実施例 4 に準ずる方法で素子を作成した。

- 5 ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $1 \text{ mA/cm}^2$  の電流が流れ、輝度約  $30 \text{ cd/m}^2$ 、波長  $464 \text{ nm}$  の青色の発光を得た。

## (実施例 8)

- 10 実施例 4 で用いた透明支持基板を蒸着装置の基板ホルダーに固定しNPDをいれた石英るつぼ、式 (10) で表される化合物を入れた石英るつぼ、アルミニウムを入れたタングステン製のるつぼ、およびフッ化リチウムを入れたタングステン製のるつぼを装着した。

- 15 真空槽を  $1 \times 10^{-3} \text{ Pa}$  まで減圧し、NPD入りのるつぼを加熱して、膜厚  $50 \text{ nm}$  になるようにNPDを蒸着して正孔輸送層を形成し、次いで、式 (10) で表される化合物入りのるつぼを加熱して、膜厚  $50 \text{ nm}$  になるように蒸着して電子輸送性発光層を形成した。蒸着速度は  $0.1 \sim 0.2 \text{ nm/秒}$  であった。

- 20 その後真空槽を  $2 \times 10^{-4} \text{ Pa}$  まで減圧し、タングステン製のるつぼを加熱して、フッ化リチウムを  $2 \text{ nm}$  有機層の上に蒸着し、最後にアルミニウムを  $100 \text{ nm}$  蒸着し、有機EL素子を得た。

ITO電極を陽極、アルミニウム電極を陰極として、直流電圧を印加すると、約  $2 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長  $515 \text{ nm}$  の緑色の発光を得た。

## 25 (実施例 9)

実施例 8 で用いた式 (10) で表される化合物を、式 (4) で表される化合物に替えた以外は、実施例 8 に準ずる方法で素子を作成した。

ITO電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $2 \text{ mA/cm}^2$  の電流が流れ、輝度約  $15 \text{ cd/m}^2$ 、波長  $616$

nmの赤色の発光を得た。

(実施例 10)

実施例 4 で用いた式 (10) で表される化合物を、前記の式 (9) で表される  
5 化合物に替えた以外は、実施例 4 に準ずる方法で素子を作成した。

I TO 電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印  
加すると、約  $2 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長  $477 \text{ nm}$  の青色の発光を得た。

10 (実施例 11)

実施例 4 で用いた式 (10) で表される化合物を、前記の式 (12) で表され  
る化合物に替えた以外は実施例 4 に準ずる方法で素子を作成した。

I TO 電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印  
加すると、約  $0.7 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長  $511 \text{ nm}$  の緑色の発光を得た。  
15

(実施例 12)

実施例 4 で用いた式 (10) で表される化合物を、前記の式 (13) で表され  
る化合物に替えた以外は実施例 4 に準ずる方法で素子を作成した。

20 I TO 電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印  
加すると、約  $30 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長  $622 \text{ nm}$  の赤色の発光を得た。

(実施例 13)

25 実施例 4 で用いた透明支持基板を蒸着装置の基板ホルダーに固定し NPD をい  
れた石英るつぼ、式 (10) で表される化合物を入れた石英るつぼ、式 (11)  
で表される化合物を入れた石英るつぼ、PYPY を入れた石英るつぼ、アルミニ  
ウムを入れたタングステン製のるつぼ、およびフッ化リチウムを入れたタングス  
テン製のるつぼを装着した。

真空槽を  $1 \times 10^{-3}$  Pa まで減圧し、NPD入りのるつぼを加熱して、膜厚 50 nm になるように NPD を蒸着して正孔輸送層を形成し、次いで、式 (10) および (11) で表される化合物入りのるつぼを加熱して、膜厚 15 nm になるように蒸着して発光層を形成し、次いで、PPPY入りのるつぼを加熱して、膜厚 35 nm になるように PPPY を蒸着して電子輸送層を形成した。この際、発光層のそれぞれの化合物の組成比は、式 (10) で表わされる化合物が 2 %、式 (11) で表わされる化合物が 98 % になるようにした。

その後真空槽を  $2 \times 10^{-4}$  Pa まで減圧し、タングステン製のるつぼを加熱して、フッ化リチウムを 0.5 nm 有機層の上に蒸着し、最後にアルミニウムを 100 nm 蒸着し、有機 EL 素子を得た。

ITO 電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $1 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長 495 nm の青緑色の発光を得た。

#### (実施例 14)

実施例 13 で用いた式 (10) で表される化合物を式 (14) で表される化合物に、式 (11) で表される化合物をトリス 8-ヒドロキシキノリンアルミニウムに替えた以外は、実施例 13 に準ずる方法で素子を作成した。

ITO 電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約  $20 \text{ mA/cm}^2$  の電流が流れ、輝度約  $100 \text{ cd/m}^2$ 、波長約 600 nm の赤色の発光を得た。

#### 産業上の利用可能性

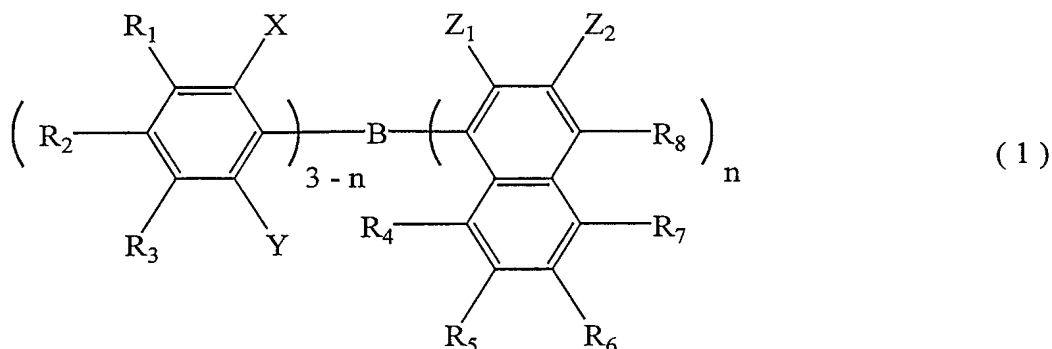
本発明の新規な化合物であるボラン誘導体は、固体状態での発光効率が高いので、発光材料として好適である。また、電子写真、非線形光学材料および導電性材料などの光電子機能材料としても有用である。

また、本発明の有機 EL 素子は、発光効率の高い発光材料を使用しているために、これを用いた場合、低消費電力で長寿命なディスプレイが作成できる。

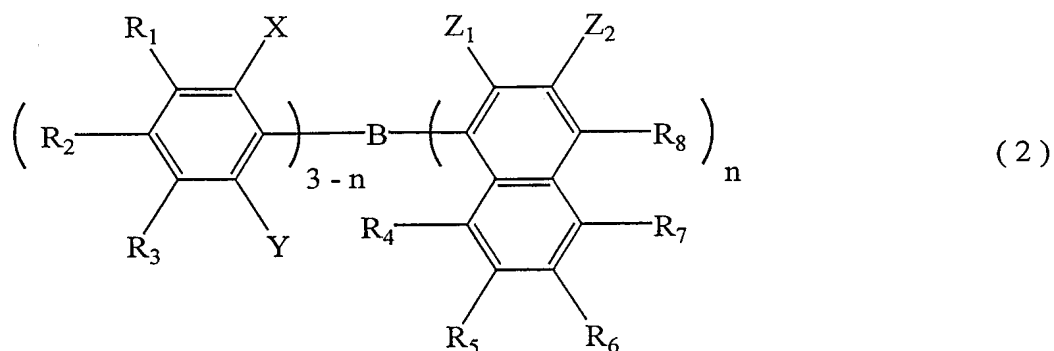


## 請求の範囲

1. 式(1)で表されるボラン誘導体。



- 5 (式中、 $R_1 \sim R_8$ および $Z_2$ は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、 $X$ 、 $Y$ および $Z_1$ は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、 $Z_1$ と $Z_2$ の置換基は相互に結合して縮合環を形成してもよく、 $n$ は1～3の整数を示し、 $n$ が2以上の場合、 $Z_1$ は異なってもよい。但し、 $n$ が1、 $X$ 、 $Y$ および $R_2$ がメチル基であって、 $R_8$ が水素原子または置換ボリル基の場合、および $n$ が3で $Z_1$ がメチル基の場合を含まない。)
- 10 2. ボロン原子に対して少なくとも1個の置換もしくは無置換の9-アンスリル基が結合している、請求項1に記載のボラン誘導体。
- 15 3. 式(2)で表されるボラン誘導体を用いた発光材料。



(式中、 $R_1 \sim R_8$ および $Z_2$ は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、 $X$ 、 $Y$ および $Z_1$ は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、 $Z_1$ と $Z_2$ の置換基は相互に結合して縮合環を形成してもよく、 $n$ は1～3の整数を示し、 $n$ が2以上の場合、 $Z_1$ は異なってもよい。)

4. ボラン誘導体が、ボロン原子に対して少なくとも1個の置換もしくは無置換の9-アンスリル基が結合している化合物である、請求項3に記載の発光材料。
5. 請求項3に記載の式(2)で表されるボラン誘導体を用いた電荷輸送材料。
6. ボラン誘導体が、ボロン原子に対して少なくとも1個の置換もしくは無置換の9-アンスリル基が結合している化合物である、請求項5に記載の電荷輸送材料。
7. 請求項3に記載の式(2)で表されるボラン誘導体を用いた有機電界発光素子。
8. 式(2)で表されるボラン誘導体の1種もしくは2種以上の混合物、または式(2)で表されるボラン誘導体の1種以上と式(2)で表されるボラン誘導体以外の発光材料の1種以上との混合物を発光層に用いた、請求項7に記載の有機電界発光素子。
9. 式(2)で表されるボラン誘導体を電荷輸送層に用いた、請求項7に記載の

有機電界発光素子。

10. ボラン誘導体が、ボロン原子に対して少なくとも1個の置換もしくは無置換の9-アンスリル基が結合している化合物である、請求項7乃至9のいずれか1項に記載の有機電界発光素子。

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/07219

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl<sup>7</sup> C07F5/02, C09K11/06, H05B33/14, H05B33/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl<sup>7</sup> C07F5/02, C09K11/06, H05B33/14, H05B33/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS (STN), REGISTRY (STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP, 775706, A2 (Ciba Specialty Chemicals Holding Inc.), 28 May, 1997 (28.05.97) & JP, 9-188684, A & US, 5807905, A	1~2 3~10
X A	BLOUNT, John F. et al., "Conformational analysis of triarylboranes", J. Amer. Chem. Soc., 1973, Vol.95 No.21, p.7019-7029	1~2 3~10
A	WO, 98/36035, A1 (QUEEN'S UNIVERSITY AT KINGSTON), 20 August, 1998 (20.08.98) & AU, 9859780, B	1~10

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not  
considered to be of particular relevance

"E" earlier document but published on or after the international filing  
date

"L" document which may throw doubts on priority claim(s) or which is  
cited to establish the publication date of another citation or other  
special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other  
means

"P" document published prior to the international filing date but later  
than the priority date claimed

"T" later document published after the international filing date or  
priority date and not in conflict with the application but cited to  
understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be  
considered novel or cannot be considered to involve an inventive  
step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be  
considered to involve an inventive step when the document is  
combined with one or more other such documents, such  
combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search  
03 April, 2000 (03.04.00)

Date of mailing of the international search report  
11 April, 2000 (11.04.00)

Name and mailing address of the ISA/  
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

## A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int.Cl.<sup>7</sup> C07F5/02, C09K11/06, H05B33/14, H05B33/22

## B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int.Cl.<sup>7</sup> C07F5/02, C09K11/06, H05B33/14, H05B33/22

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース (データベースの名称、調査に使用した用語)

CAPLUS (STN), REGISTRY (STN)

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X A	EP, 775706, A2 (Ciba Specialty Chemicals Holding Inc.) 28. 5月. 1997 (28. 05. 97) &JP, 9-188684, A &US, 5807905, A	1 ~ 2 3 ~ 10
X A	BLOUNT, John F. et al., "Conformational analysis of triarylb oranes", J. Amer. Chem. Soc., 1973, Vol. 95 No. 21, p. 7019-7029	1 ~ 2 3 ~ 10
A	WO, 98/36035, A1 (QUEEN'S UNIVERSITY AT KINGSTON) 20. 8月. 1998 (20. 08. 98) &AU, 9859780, B	1 ~ 10

☐ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

## \* 引用文献のカテゴリー

「A」 特に関連のある文献ではなく、一般的技術水準を示すもの  
「E」 国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの  
「L」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)  
「O」 口頭による開示、使用、展示等に言及する文献  
「P」 国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献

「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&amp;」 同一パテントファミリー文献

国際調査を完了した日

03. 04. 00

国際調査報告の発送日

11.04.00

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)

郵便番号 100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

本堂 裕司

4 H

9049

電話番号 03-3581-1101 内線 3443

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number  
**WO 00/73307 A2**

(51) International Patent Classification<sup>7</sup>: **C07D 473/00**

Apartment 504, Silver Spring, MD 20902 (US). **KIM, Yong-Chul** [KR/US]; Apartment 202, 12407 Village Square Terrace, Rockville, MD 20852 (US).

(21) International Application Number: PCT/US00/15233

(22) International Filing Date: 1 June 2000 (01.06.2000)

(74) Agent: **VIKSINNS, Ann, S.**; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/505,504	1 June 1999 (01.06.1999)	US
60/136,898	1 June 1999 (01.06.1999)	US
60/136,900	1 June 1999 (01.06.1999)	US
60/151,875	31 August 1999 (31.08.1999)	US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **UNIVERSITY OF VIRGINIA PATENT FOUNDATION** [US/US]; Suite 1-110, 1224 West Main Street, Charlottesville, VA 22903-2442 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants and

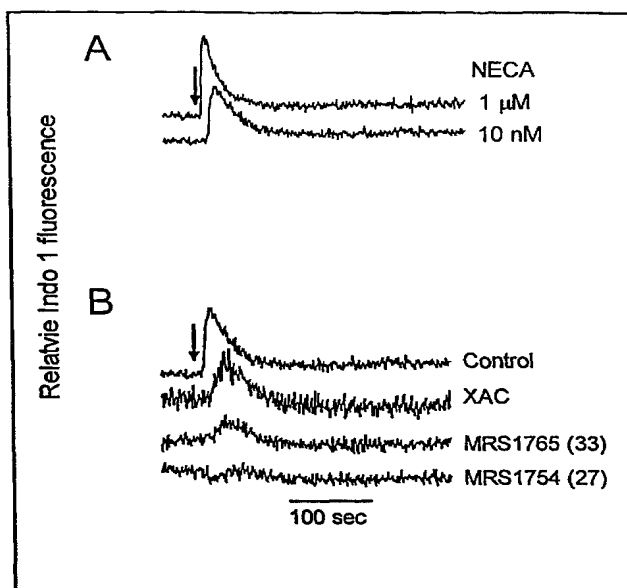
(72) Inventors: **LINDEN, Joel, M.** [US/US]; 207 Harvest Drive, Charlottesville, VA 22903 (US). **JOCOBSON, Kenneth, A.** [US/US]; 1111 University Boulevard West,

Published:

— Without international search report and to be republished upon receipt of that report.

[Continued on next page]

(54) Title: SUBSTITUTED 8-PHENYLYXANTHINES USEFUL AS ANTAGONISTS OF A<sub>2B</sub> ADENOSINE RECEPTORS



(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A<sub>2B</sub> adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.



---

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**SUBSTITUTED 8-PHENYLYXANTHINES USEFUL AS  
ANTAGONISTS OF A<sub>2B</sub> ADENOSINE RECEPTORS**

5

Cross-Reference to Related Applications

This application claims priority of U.S. provisional patent applications Serial Nos. 60/136,898 filed June 1, 1999, 60/136,900 filed June 1, 1999, 60/151,875 filed August 31, 1999, and 09/505,504 filed February 17, 2000.

10

Government Funding

The invention described herein was made with government support under Grant Numbers HL37942 and HL56111 awarded by the National Institute of Health. The United States Government has certain rights in the invention.

15

Field of the Invention

The present invention relates to compounds and pharmaceutical compositions that are selective antagonists of A<sub>2B</sub> adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

20

Background of the Invention

The alkylxanthine theophylline (compound 1, Figure 1), a weak non-selective adenosine antagonist (See Linden, J., *et al.*, in *Cardiovascular Biology of Purines*, eds. G. Burnstock, *et al.*, 1998, pp 1-20.) is useful therapeutically for the treatment of asthma. However, its use is associated with unpleasant side effects, such as insomnia and diuresis. (See Vassallo, R. *et al.*, *Mayo. Clin. Proc.* 1998, 73, 346-354.) In recent years, the use of theophylline as a bronchodilator, for relief of asthma, has been supplanted by drugs of other classes, *i.e.*, selective  $\beta_2$ -adrenergic agonists, corticosteroids, and recently leukotriene antagonists. (See Drazen, J. M., *et al.*, *New Eng. J. Med.* 1999, 340, 197-206.) These compounds also have limitations, thus, the development of a theophylline-like drug with reduced side effects is still desirable.

30

It has been recognized that theophylline and its closely related analogue caffeine block endogenous adenosine acting as a local modulator of adenosine



receptors in the brain and other organs at therapeutically useful doses.

Adenosine activates four subtypes of G protein-coupled adenosine receptors (ARs),  $A_1/A_{2A}/A_{2B}/A_3$ . (See Fredholm, B. B., *et al.*, *Pharmacol. Rev.* **1999**, *51*, 83-133.) In comparison to the other known actions of theophylline, *e.g.*,

- 5 inhibition of phosphodiesterases, theophylline is more potent in antagonism of adenosine receptors. Enprofylline, (compound **3**, Figure 1) a compound that is used to treat asthma, is another example of a xanthine that has been reported to block  $A_{2B}$  adenosine receptors. However, this compound only weakly blocks  $A_1$ ,  $A_{2A}$  and  $A_3$  adenosine receptors.

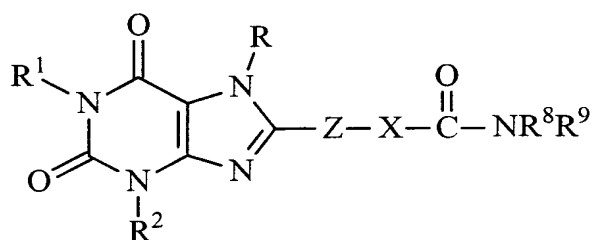
- 10 It has been reported that therapeutic concentrations of theophylline or enprofylline block human  $A_{2B}$  receptors, and it has been proposed that antagonists selective for this subtype may have potential use as antiasthmatic agents. (See Feoktistov, I., *et al.*, *Pharmacol. Rev.* **1997**, *49*, 381-402; and Robeva, A.S., *et al.*, *Drug Dev. Res.* **1996**, *39*, 243-252. Enprofylline has a
- 15 reported  $K_i$  value of 7  $\mu$ M and is somewhat selective in binding to human  $A_{2B}$  ARs. (See Robeva, A.S., *et al.*, *Drug Dev. Res.* **1996**, *39*, 243-252 and Linden, J., *et al.*, *Mol. Pharmacol.* **1999**, *56*, 705-713.)  $A_{2B}$  ARs are expressed in some mast cells, such as the BR line of canine mastocytoma cells, which appear to be responsible for triggering acute  $Ca^{2+}$  mobilization and degranulation. (See
- 20 Auchampach, J.A., *et al.*, *Mol. Pharmacol.* **1997**, *52*, 846-860 and Forsyth, P., *et al.*, *Inflamm. Res.* **1999**, *48*, 301-307.)  $A_{2B}$  ARs also trigger  $Ca^{2+}$  mobilization, and participate in a delayed IL8 release from human HMC-1 mast cells. Other functions associated with the  $A_{2B}$  AR are the control of cell growth and gene expression, (See Neary, J., *et al.*, *Trends Neurosci.* **1996**, *19*, 13-18.) endothelial-
- 25 dependent vasodilation (See Martin, P.L., *et al.*, *J. Pharmacol. Exp. Ther.* **1993**, *265*, 248-253.), and fluid secretion from intestinal epithelia. (See Strohmeier, G.R., *et al.*, *J. Biol. Chem.* **1995**, *270*, 2387-2394.) Adenosine acting through  $A_{2B}$  ARs has also been reported to stimulate chloride permeability in cells expressing the cystic fibrosis transport regulator. (See Clancy, J.P., *et al.*, *Am. J.*
- 30 *Physiol.* **1999**, *276*, C361-C369.)

Although adenosine receptor subtype-selective probes are available for the  $A_1$ ,  $A_{2A}$ , and  $A_3$  ARs, only few weakly selective antagonists and no selective

agonists are known for the A<sub>2B</sub> receptor. Therefore, a continuing need exists for compounds that are selective A<sub>2B</sub> receptor antagonists.

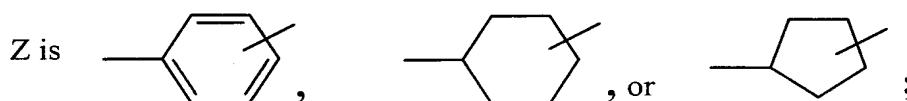
### Summary of the Invention

- 5 The present invention provides compounds that act as antagonists of A<sub>2B</sub> adenosine receptors. Accordingly, the present invention provides a compound of formula I:



I

- wherein R, and R¹ are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl,  
 10 (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



- X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein one of the  
 15 carbon atoms in the alkylene, alkenylene or alkynylene groups can be replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—, wherein

- R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>8</sub>)heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-  
 20 C<sub>10</sub>)heteroaryl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl or (C<sub>7</sub>-C<sub>18</sub>)aralkyl, optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —CO<sub>2</sub>H, and —SO<sub>3</sub>H, wherein

- $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl, wherein  $R^8$  is hydrogen,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or
- 5 more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or
- $R^8$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents
- 10 independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or
- $R^8$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents
- 15 independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; and
- wherein  $R^9$  is  $-NR^{10}R^{11}$ , or  $R^9$  is  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or
- 25  $R^9$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or
- 30  $R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,

—CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H, and

wherein R<sup>10</sup> and R<sup>11</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
(C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle,  
5 heteroaryl, —C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)CR<sup>21</sup>=CR<sup>22</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)R<sup>12</sup>,  
—C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl or —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkenyl, each optionally  
substituted with one or more substituents, wherein the substituents independently  
are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)-  
aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>,  
10 —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or  
—SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom can be taken together  
to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted  
with one or more substituents, wherein the substituents independently are oxo,  
(C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
15 heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
—NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;  
wherein n is 1 to 6, and m is 0 to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl,  
(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, hetero-  
20 cycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more  
substituents independently selected from the group consisting of oxo,  
(C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
25 —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H.

The R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> groups are  
independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,  
(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and the R<sup>21</sup> and R<sup>22</sup> groups are  
independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,  
30 (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl.

The invention also provides pharmaceutically acceptable salts of a  
compound of formula I. The invention also provides a pharmaceutical  
composition comprising a compound of formula I or a pharmaceutically

acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity, *i.e.*, over-activity, of adenosine A<sub>2B</sub> receptors is implicated in one or more symptoms of the pathology and antagonism (*i.e.*, blocking) of their activity is desired to ameliorate said symptoms. Such diseases or conditions include, but are not limited to, asthma, diarrheal diseases, insulin resistance, diabetes, prevention of mast cell degranulation associated with ischemia/reperfusion injuries, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy. The invention also includes a method for treating asthma, diarrheal diseases, insulin resistance, diabetes, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy in a mammal, (*e.g.*, a human) comprising administering to the mammal in need of such therapy, an effective amount of at least one compound of formula I or pharmaceutically acceptable salt(s) thereof.

The invention provides a compound of formula I for use in medical therapy preferably for use in treating diseases or conditions associated with deleterious A<sub>2B</sub> receptor activation or activity, including asthma, diarrheal diseases, insulin resistance, diabetes, ischemic/reperfusion injury, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy, as well as the use of a compound of formula I for the manufacture of a medicament for the treatment of a pathological condition or symptom in a mammal, such as a human, which is associated with deleterious A<sub>2B</sub> receptor activation or activity, including the above-referenced diseases or pathologies.

The invention also includes a method comprising contacting a compound of formula I, optionally having a radioactive isotope (radionuclide), such as, for example, tritium, radioactive iodine (for example, <sup>125</sup>I for binding assays or <sup>123</sup>I for Spect Imaging) and the like, with target A<sub>2B</sub> adenosine receptor sites comprising said receptors, *in vivo* or *in vitro*, so as to bind said receptors. Cell membranes comprising bound A<sub>2B</sub> adenosine receptor sites can be used to

measure the selectivity of test compounds for adenosine receptor subtypes or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with A<sub>2B</sub>-receptor mediation, by contacting said agents with said radioligands and receptors, and measuring the extent of displacement of the radioligand and/or binding of the agent.

#### Brief Description of the Figures

Figure 1 illustrates structures of various xanthines that act as antagonists at A<sub>2B</sub> receptors.

Figure 2 is a graphic illustration of the inhibition by several selective A<sub>2B</sub> AR antagonists of NECA-stimulated calcium mobilization in HEK-A<sub>2B</sub> cells. Cells were loaded with Indo 1 for 1 hour. The A) curves indicate calcium mobilization in response to 10 nM and 1  $\mu$ M NECA added at the arrow. The B) curves indicate calcium mobilization in response to 10 nM NECA added at the arrow in cells pretreated for two minutes with 1% DMSO (control) or with 100 nM of the indicated antagonists. The results are typical of replicate experiments.

Figure 3 illustrates the synthesis of amide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 4 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 5 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 6 illustrates the experimental protocol for the ninety minute cardiac left anterior descending (LAD) coronary artery occlusion/reperfusion test. Regional myocardial blood flow was measured at 30 second, 90 second, 3 minute, 5 minute, 8 minute, 13 minute, 23 minute, 38 minute, and 68 minute, intervals, using radioactive microspheres (mic), administered at the times indicated.

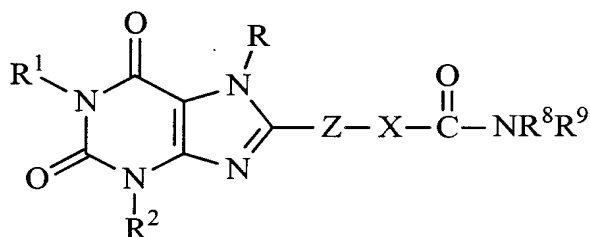
Figure 7 illustrates the regional myocardial transmural blood flow in the central infarct (solid bar), border (open bar), and normal (striped bar) zones at baseline, during the LAD occlusion, and 2 hrs after reperfusion. During the total LAD occlusion, mean flow of test solution was < 0.2 ml/min/g for 90 min.

Figure 8 illustrates the mean infarct size measured using triphenyl tetrazolium chloride (TTC) staining in vehicle-treated (control) dogs and in dogs treated with 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (**27**). The *p*-cyanoanilide, **27**, (200 nM) was infused  
 5 intracoronary at a rate of 1 ml/min during occlusion and reperfusion. The treatment prevented or markedly attenuate the extent of myocardial infarction and significantly reduced the infarct area (IA), measured as % left ventricle area (%LV) or % area at risk (%RA).

Figure 9 illustrates the results the specific and nonspecific binding of test  
 10 compound 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (**27**). The graph shows both specific and nonspecific binding.

#### Detailed Description of the Invention

In one embodiment the present invention provides compounds of  
 15 formula I:



I

wherein R, and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>3</sub>-C<sub>8</sub>)heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or (C<sub>6</sub>-C<sub>10</sub>)heteroaryl,



and X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene. In the X groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula  $\text{—O—}$ ,  $\text{—N(R}^4\text{)C(O)—}$ ,  $\text{—OC(O)—}$ ,  $\text{—N(R}^5\text{)(R}^6\text{)—}$ ,  $\text{—S—}$ ,  $\text{—S(O)—}$  or  $\text{—SO}_2\text{—}$ , wherein

$\text{R}^2$  is hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkynyl}$ ,  $(\text{C}_1\text{—C}_8)\text{alkoxy}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_3\text{—C}_8)\text{heterocycle}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_6\text{—C}_{10})\text{heteroaryl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$  or  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ ; optionally substituted with one or more substituents selected from the group consisting of  $\text{—OH}$ ,  $\text{—SH}$ ,  $\text{—NH}_2$ ,  $\text{—NHR}^7$ ,  $\text{—CN}$ ,  $\text{—CO}_2\text{H}$ , and  $\text{—SO}_3\text{H}$ , wherein

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are independently hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$  or halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ .

$\text{R}^8$  is hydrogen,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_1\text{—C}_8)\text{alkoxy}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl, halo,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , substituted with one or more substituents independently selected from the group consisting of oxo,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_6\text{—C}_{10})\text{aryl}$ , substituted with one or more substituents independently selected from the group consisting of  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; and

wherein  $\text{R}^9$  is  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ; or

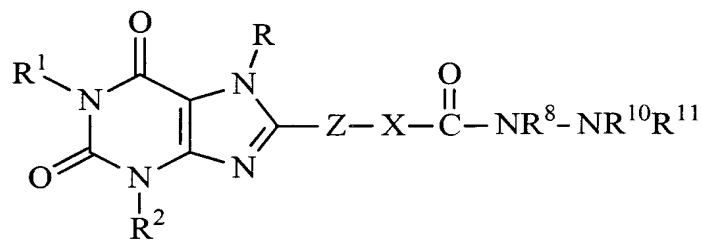


$R^9$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  
 5  $-SO_2R^{20}$  and  $-SO_3H$ ; or

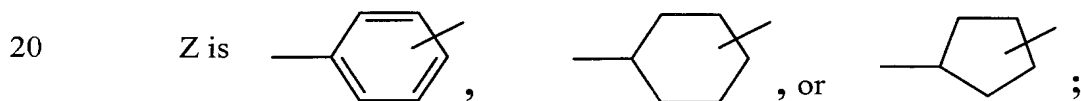
$R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
 10  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ .

The  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{23}$  and  $R^{24}$  groups are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl.

In another embodiment the present invention provides compounds of  
 15 formula II:



wherein  $R$ , and  $R^1$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl,  $(C_1-C_8)$ alkoxy,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_3-C_8)$ heterocycle,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or  $(C_6-C_{10})$ heteroaryl,



and  $X$  is  $(C_1-C_8)$ alkylene,  $(C_2-C_8)$ alkenylene,  $(C_2-C_8)$ alkynylene. In the  $X$  groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula  $\text{—O—}$ ,  $\text{—N(R}^4\text{)C(O)—}$ ,  $\text{—OC(O)—}$ ,  $\text{—N(R}^5\text{)(R}^6\text{)—}$ ,  $\text{—S—}$ ,  $\text{—S(O)—}$  or  $\text{—SO}_2\text{—}$ , wherein

$\text{R}^2$  group is hydrogen,  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkynyl}$ ,  $(\text{C}_1\text{--C}_8)\text{alkoxy}$ ,  $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$ ,  $(\text{C}_3\text{--C}_8)\text{heterocycle}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_6\text{--C}_{10})\text{heteroaryl}$ ,  $(\text{C}_4\text{--C}_{16})\text{cycloalkylalkyl}$  or  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ ; optionally substituted with one or more substituents selected from the group consisting of  $\text{—OH}$ ,  $\text{—SH}$ ,  $\text{—NH}_2$ ,  $\text{—NHR}^7$ ,  $\text{—CN}$ ,  $\text{—CO}_2\text{H}$ , and  $\text{—SO}_3\text{H}$ , wherein  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are independently hydrogen,  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$  or  $\text{halo}(\text{C}_1\text{--C}_6)\text{alkyl}$ .

$\text{R}^8$  is hydrogen,  $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{--C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $(\text{C}_1\text{--C}_8)\text{alkoxy}$ ,  $\text{halo}(\text{C}_1\text{--C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heteroaryl, halo,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_1\text{--C}_8)\text{alkyl}$ , substituted with one or more substituents independently selected from the group consisting of oxo,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_6\text{--C}_{10})\text{aryl}$ , substituted with one or more substituents independently selected from the group consisting of  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $\text{halo}(\text{C}_1\text{--C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; and

wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently hydrogen,  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—C(O)(CH}_2\text{)}_n\text{CO}_2\text{R}^{12}$ ,  $\text{—C(O)CR}^{21}\text{=CR}^{22}\text{(CH}_2\text{)}_m\text{CO}_2\text{R}^{12}$ ,  $\text{—C(O)R}^{12}$ ,  $\text{—C(O)(C}_3\text{--C}_8)\text{cycloalkyl}$  or  $\text{—C(O)(C}_3\text{--C}_8)\text{cycloalkenyl}$ , each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{--C}_8)\text{alkyl}$ ,  $\text{halo}(\text{C}_1\text{--C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{--C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{--C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{--C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or

—SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
 5 —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; wherein n is 1 to 6, and m is 0 to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, hetero-  
 10 cycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
 15 —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H.

The R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and the R<sup>21</sup> and R<sup>22</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl,  
 20 (C<sub>7</sub>-C<sub>18</sub>)aralkyl.

Preferred compounds of the invention exclude compounds of formula I wherein —NR<sup>8</sup>R<sup>9</sup> is aminoalkyl, aminodialkyl or hydrazino. Preferred compounds of the invention also exclude compounds of formula I wherein R and R<sup>8</sup> are both H, and R<sup>1</sup> and R<sup>2</sup> are both alkyl, and R<sup>9</sup> is 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl.  
 25

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

30 The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such

as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

Heteroaryl encompasses a radical attached via a ring carbon of a  
 5 monocyclic aromatic ring containing 5-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom,  
 10 particularly a benz-derivative or one derived by fusing a propylene, trimethylene or tetramethylene diradical thereto.

The term heterocycle encompasses a cyclic radical attached via a ring carbon or nitrogen of a monocyclic or bicyclic ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four  
 15 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds (*e.g.*, —CH=CH— or —CH=N—). Heterocycle includes, for example, tetrahydrofuryl, dihydrofuryl, tetrahydroimidazolyl, azanorbornyl, pyrrolidinyl, piperidinyl, piperizinyl, and the like.

Specifically, (C<sub>1</sub>-C<sub>8</sub>)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, isopentyl, 3-pentyl, hexyl, heptyl or octyl;  
 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; (C<sub>4</sub>-C<sub>12</sub>)cycloalkylalkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-  
 25 cyclobutylethyl, 2-cyclopentylethyl or 2-cyclohexylethyl; (C<sub>1</sub>-C<sub>8</sub>)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptyloxy or octyloxy; (C<sub>2</sub>-C<sub>8</sub>)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-  
 30 heptenyl, 1-octenyl, 2-octenyl, 3-octenyl or 4-octenyl; (C<sub>2</sub>-C<sub>8</sub>)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1-heptylnyl, 2-heptylnyl, 3-heptylnyl, 1-octynyl, 2-octynyl or 3-octynyl; halo(C<sub>1</sub>-C<sub>6</sub>)alkyl can be

iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; (C<sub>6</sub>-C<sub>10</sub>)aryl can be phenyl, indenyl or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

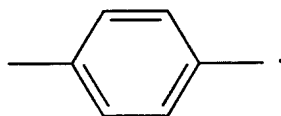
The term "amino acid," comprises the residues of the natural amino acids (*e.g.*, Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (*e.g.*, phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline,  $\alpha$ -methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (*e.g.*, acetyl, benzyl, COCF<sub>3</sub> or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (*e.g.*, as a (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl or benzyl ester or amide; or as an  $\alpha$ -methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis*, Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). An amino acid can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine.

The term "peptide" comprises the residues two or more of the natural amino acids, as well as unnatural amino acids or a mixture thereof, that are linked through an amide bond. The term also comprises peptides that are protected at the carboxy terminus (*e.g.*, as a (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl or benzyl ester or amide; or as an  $\alpha$ -methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis*, Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). A

peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine. Preferably, the peptide has less than 30 amino acid residues, more preferably less than 20 residues, and most preferably from about 2 to about 5 residues.

The preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, iso-butyl, and sec-butyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, and 3-hexyl. The preferred alkylene groups are methylene, ethylene, propylene, butylene, pentylene, and hexylene. The preferred alkenyl groups are vinyl, 1-propenyl, 2-propenyl (allyl), 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, and 3-hexenyl. The preferred alkenylene groups are ethenylene, propenylene, butenylene, pentenylene, and hexenylene. The preferred alkynyl groups are ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, 5-hexyne. The preferred alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, and sec-butoxy. The preferred cycloalkyl groups are cyclopentyl, and cyclohexyl. The preferred cycloalkylalkyl groups are, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentylethyl, and 2-cyclohexylethyl. The preferred aryl groups are phenyl, indenyl or naphthyl. The preferred aralkyl groups are benzyl and 2-phenylethyl. The preferred haloalkyl groups are iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl. The preferred heteroaryl groups are furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, thiophenyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridinyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific Z substituent is :



A specific Z—X moiety is:



- 5 Specific R<sup>1</sup> and R<sup>2</sup> groups are each —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH=CH<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, or cyclohexylmethyl.

Specific R<sup>8</sup> and R<sup>9</sup> groups are each hydrogen, substituted phenyl or benzyl.

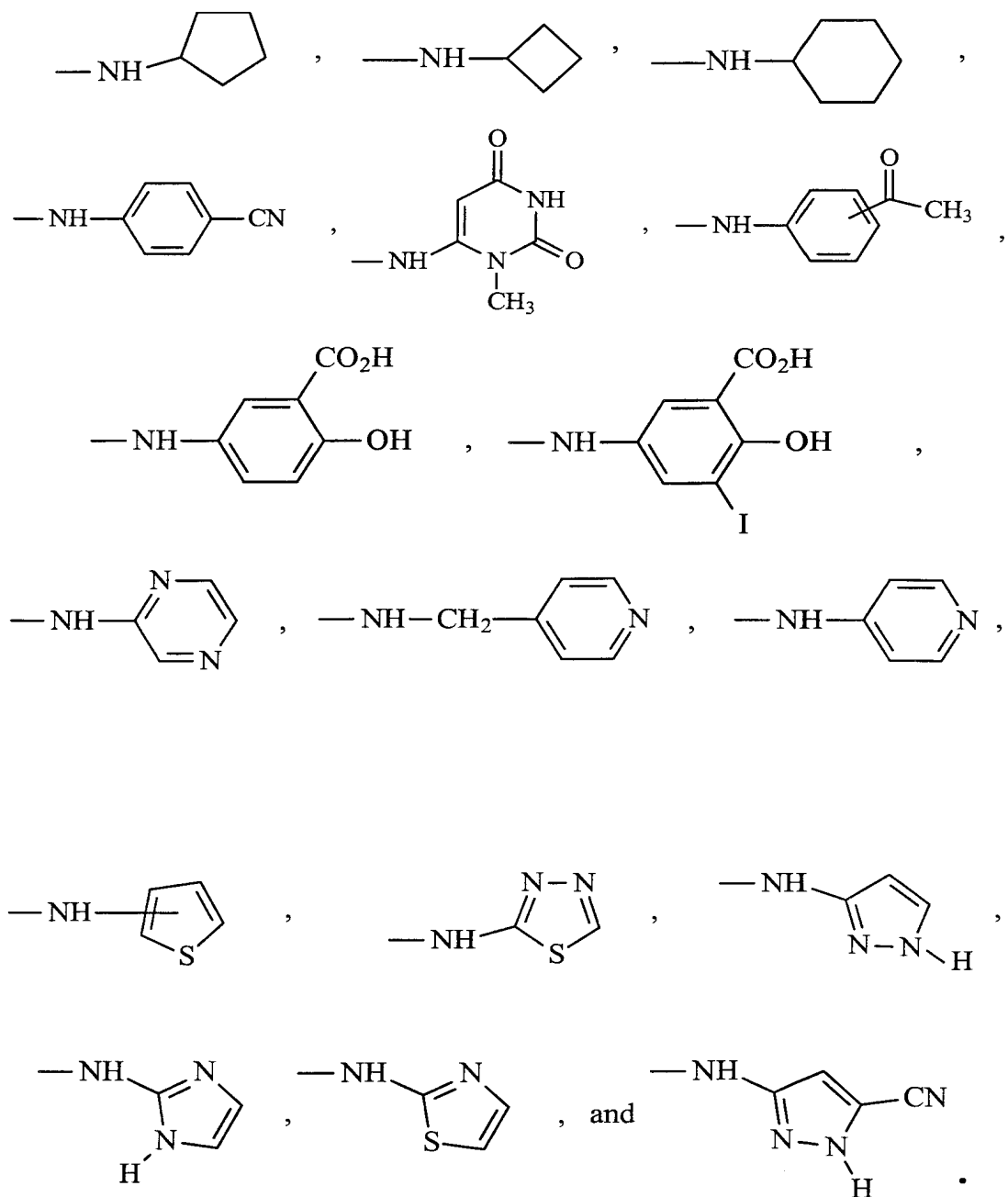
- Specific R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, and R<sup>7</sup> groups are each hydrogen, methyl, ethyl,  
 10 propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl.

- In a preferred embodiment, when the R<sup>9</sup> groups are phenyl substituted with one two or three substituents that are independently cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl,  
 15 benzyl, —OH, F, Cl, Br, I, —CN, —NO<sub>2</sub>, —C(O)OR<sup>15</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup> or —C(O)NR<sup>17</sup>R<sup>18</sup> or benzyl they can optionally be methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, benzyl, —OH, F, Cl, Br, I, —CN, —NO<sub>2</sub>, —C(O)OR<sup>15</sup>, —C(O)R<sup>16</sup> or —C(O)NR<sup>17</sup>R<sup>18</sup>, wherein  
 20 R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> are as defined above.

- The preferred R<sup>10</sup>, and R<sup>11</sup> groups are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl, —CO(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —COCR<sup>21</sup>=CR<sup>22</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>12</sup>,  
 25 —C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>–C<sub>8</sub>)cycloalkyl, —C(O)(C<sub>3</sub>–C<sub>8</sub>)cycloalkenyl, and compounds wherein the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom taken together form a ring. More preferred R<sup>10</sup>, and R<sup>11</sup> groups are independently hydrogen, —CO(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —COCR<sup>21</sup>=CR<sup>22</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>–C<sub>6</sub>)cycloalkyl and —C(O)(C<sub>3</sub>–C<sub>6</sub>)cycloalkenyl, each wherein the R<sup>10</sup>  
 30 and R<sup>11</sup> groups and the nitrogen atom taken together form (C<sub>6</sub>–C<sub>10</sub>)heterocycle or (C<sub>6</sub>–C<sub>10</sub>)heteroaryl, n is 1 to 4 and m is 0 to 2. The most preferred R<sup>10</sup>, and R<sup>11</sup> groups are independently hydrogen, —CO(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —COCH=CHCO<sub>2</sub>R<sup>12</sup>, —C(O)R<sup>12</sup>, or wherein the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom taken

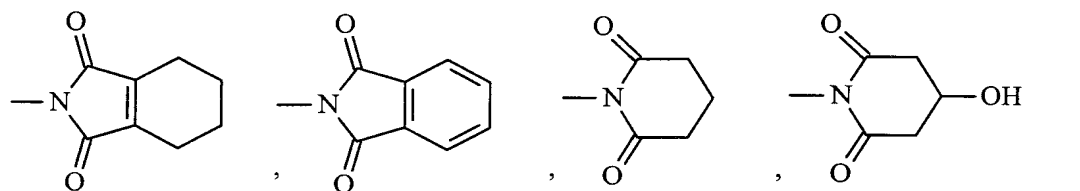
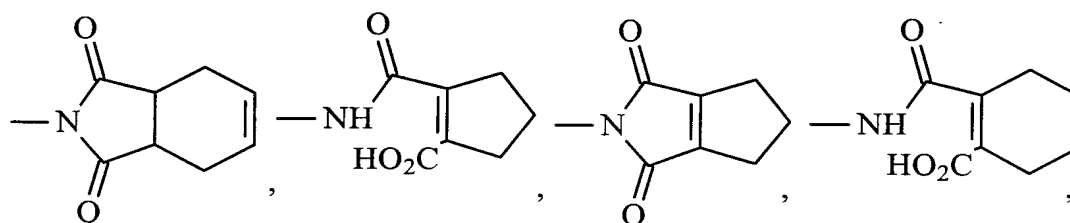
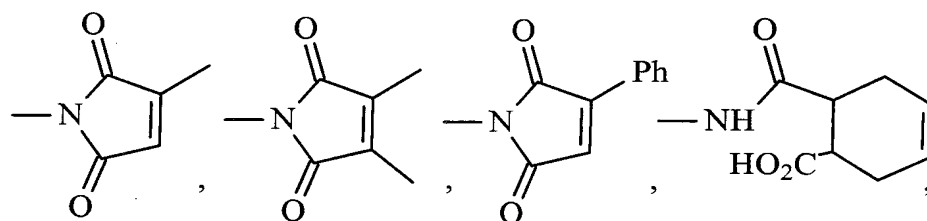
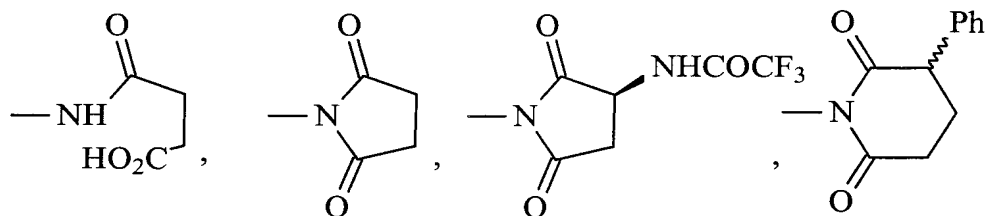
together form a ring or wherein n is 1 to 4 and  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{21}$  and  $R^{22}$  are defined above.

Specific values for  $—NR^8R^9$  are:



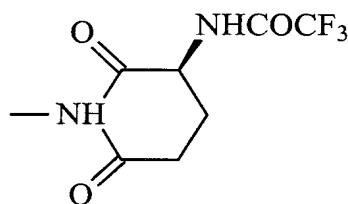


Specific values for  $\text{—NR}^{10}\text{R}^{11}$  are:



5

or



The following abbreviations have been used herein:

	[ <sup>125</sup> I]ABA	[ <sup>125</sup> I] <i>N</i> <sup>6</sup> -(4-aminobenzyl)-adenosine
	[ <sup>125</sup> I]AB-MECA	[ <sup>125</sup> I] <i>N</i> <sup>6</sup> -(4-amino-3-iodobenzyl)-adenosine-5'- <i>N</i> -methyluronamide
5	<sup>125</sup> I-ABOPX	<sup>125</sup> I-3-(4-amino-3-iodobenzyl)-8-oxyacetate-1-propyl-xanthine
	8-SPT	8-sulphophenyltheophylline
	AR	adenosine receptor
	Bn	benzyl
10	BOP-Cl	bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
	CGS 21680	2-[4-[(2-carboxyethyl)phenyl]ethyl-amino]-5'- <i>N</i> -ethylcarbamoyl adenosine
	CHA	<i>N</i> <sup>6</sup> -cyclohexyladenosine
	CHO cells	Chinese hamster ovary cells
15	CPX	8-cyclopentyl-1,3-dipropylxanthine
	DIPEA	diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	DMEM	Dulbecco modified eagle medium
	DMF	<i>N,N</i> -dimethylformamide
20	DMSO	dimethylsulfoxide
	EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
	EDTA	ethylenediaminetetraacetate
	HEK cells	human embryonic kidney cells
	HOBt	1-hydroxybenzotriazole
25	K <sub>i</sub>	equilibrium inhibition constant
	NECA	5'- <i>N</i> -( <i>N</i> -ethylcarbamoyl)adenosine
	NHS	<i>N</i> -hydroxysuccinimide ester
	<i>R</i> -PIA	<i>R</i> - <i>N</i> <sup>6</sup> -phenylisopropyladenosine
	SAR	structure-activity relationship
30	TFA	trifluoroacetic acid
	TFAA	trifluoroacetic anhydride
	Tris	tris(hydroxymethyl)aminomethane

XAC	8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine
XCC	8-[4-[[[carboxy]methyl]oxy]phenyl]-1,3-dipropylxanthine
5 ZM 241385	4-(2-[7-amino-2-{furyl}{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl)phenol

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate,  $\alpha$ -ketoglutarate, and  $\alpha$ -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis or by chromatographic separation using a chiral stationary phase). It is also conventional to determine  $A_{2B}$  adenosine antagonist activity using the standard tests described herein or using other similar tests which are well known in the art.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical, inhalation or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and

substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or  
5 its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

10 The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and  
15 stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example,  
20 by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for  
25 example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the  
30 other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying

techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, *i.e.*, when they are liquids. However, it will generally be desirable to  
5 administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the  
10 present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings or sprayed onto the  
15 affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

20 Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet *et al.* (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith *et al.* (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by  
25 comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from  
30 about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected

but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100  $\mu\text{g/kg}$ , *e.g.*, from about 10 to about 75  $\mu\text{g/kg}$  of body weight per day, such as 3 to about 50  $\mu\text{g}$  per kilogram body weight of the recipient per day, preferably in the range of 6 to 90  $\mu\text{g/kg/day}$ , most preferably in the range of 15 to 60  $\mu\text{g/kg/day}$ .

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000  $\mu\text{g}$ , conveniently 10 to 750  $\mu\text{g}$ , most conveniently, 50 to 500  $\mu\text{g}$  of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.02, to about 5  $\mu\text{M}$ , preferably, about 0.05 to 2  $\mu\text{M}$ , most preferably, about 0.1 to about 1  $\mu\text{M}$ . This may be achieved, for example, by the intravenous injection of a 0.005 to 0.5% solution of the active ingredient, optionally in saline or orally administered as a bolus containing about 1-100  $\mu\text{g}$  of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-0.1  $\mu\text{g/kg/hr}$  or by intermittent infusions containing about 1-10  $\mu\text{g/kg}$  of the active ingredient(s).

The compounds of the invention can be administered by inhalation from an inhaler, insufflator, atomizer or pressurized pack or other means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as carbon dioxide or other suitable gas. In case of a pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount. The inhalers, insufflators, atomizers are fully described in pharmaceutical reference books such as Remington's Pharmaceutical Sciences Volumes 16 (1980) or 18 (1990) Mack Publishing Co.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple

inhalations from an insufflator or by application of a plurality of drops into the eye.

The invention will now be illustrated by the following non-limiting Examples.

5

## EXAMPLES

### Pharmacology.

The ability of a compounds of the invention to act as an A<sub>2B</sub> adenosine receptor antagonists may be determined using pharmacological models which are well known to the art or using test procedures described below.

The human A<sub>2B</sub> receptor cDNA was subcloned into the expression plasmid pDoubleTrouble as described in Robeva, A. *et al.*, Biochem. Pharmacol., 51, 545-555 (1996). The plasmid was amplified in competent JM109 cells and plasmid DNA isolated using Wizard Megaprep columns (Promega Corporation, Madison, WI). A<sub>2B</sub> adenosine receptors were introduced into HEK-293 cells by means of Lipofectin as described in Felgner, P. L. *et al.*, Proc. Natl. Acad. Sci. USA, 84, 7413-7417 (1987).

### Cell culture

Transfected HEK cells were grown under 5% CO<sub>2</sub>/95% O<sub>2</sub> humidified atmosphere at a temperature of 37°C. Colonies were selected by growth of cells in 0.6 mg/mL G418. Transfected cells were maintained in DMEM supplemented with Hams F12 nutrient mixture (1/1), 10% newborn calf serum, 2 mM glutamine and containing 50 IU/mL penicillin, 50 mg/mL streptomycin, and 0.2 mg/mL Geneticin (G418, Boehringer Mannheim). Cells were cultured in 10 cm diameter round plates and subcultured when grown confluent (approximately after 72 hours).

### Radioligand binding studies.

*At A<sub>2B</sub> receptors:* Confluent monolayers of HEK-A<sub>2B</sub> cells were washed with PBS followed by ice cold Buffer A (10 mM HEPES, 10 mM EDTA, pH 7.4) with protease inhibitors (10 µg/mL benzamidine, 100 µM phenylmethanesulfonyl fluoride, and 2 µg/mL of each aprotinin, pepstatin and



leupeptin). The cells were homogenized in a Polytron (Brinkmann) for 20 s, centrifuged at 30,000 x g, and the pellets washed twice with buffer HE (10 mM HEPES, 1 mM EDTA, pH 7.4 with protease inhibitors). The final pellet was resuspended in buffer HE, supplemented with 10% sucrose and frozen in aliquots at -80°C. For binding assays membranes were thawed and diluted 5-10 fold with HE to a final protein concentration of approximately 1 mg/mL. To determine protein concentrations, membranes, and bovine serum albumin standards were dissolved in 0.2% NaOH/0.01% SDS and protein determined using fluorescamine fluorescence. Stowell, C. P. *et al.*, *Anal. Biochem.*, **85**, 572-580 (1978).

Saturation binding assays for human A<sub>2B</sub> adenosine receptors were performed with [<sup>3</sup>H]ZM214,385 (17 Ci/mmol, Tocris Cookson, Bristol UK) (Ji, X. *et al.*, *Drug Design Discov.*, **16**, 216-226 (1999)) or <sup>125</sup>I-ABOPX (2200 Ci/mmol). To prepare <sup>125</sup>I-ABOPX, 10 µL of 1 mM ABOPX in methanol/1 M NaOH (20:1) was added to 50 µL of 100 mM phosphate buffer, pH 7.3. One or 2 mCi of Na<sup>125</sup>I was added, followed by 10 µL of 1 mg/mL chloramine-T in water. After incubation, 20 minutes at room temperature, 50 µL of 10 mg/mL Na-metabisulfite in water was added to quench the reaction. The reaction mixture was applied to a C18 HPLC column, eluting with a mixture of methanol and 5 mM phosphate, pH 6.0. After 5 min at 35% methanol, the methanol concentration was ramped to 100% over 15 min. Unreacted ABOPX eluted in 11-12 minutes; <sup>125</sup>I-ABOPX eluted at 18-19 min in a yield of 50-60% with respect to the initial <sup>125</sup>I.

In equilibrium binding assays the ratio of <sup>127</sup>I/<sup>125</sup>I-ABOPX was 10-20/1. Radioligand binding experiments were performed in triplicate with 20-25 µg membrane protein in a total volume of 0.1 mL HE buffer supplemented with 1 U/mL adenosine deaminase and 5 mM MgCl<sub>2</sub>. The incubation time was 3 h at 21°C. Nonspecific binding was measured in the presence of 100 µM NECA. Competition experiments were carried out using 0.6 nM <sup>125</sup>I-ABOPX. Membranes were filtered on Whatman GF/C filters using a Brandel cell harvester (Gaithersburg, MD) and washed 3 times over 15-20 seconds with ice cold buffer (10 mM Tris, 1 mM MgCl<sub>2</sub>, pH 7.4). B<sub>max</sub> and K<sub>D</sub> values were calculated by Marquardt's nonlinear least squares interpolation for single a site

binding models. Marquardt, D. M., *J. Soc. Indust. Appl. Math.*, **11**, 431-441.21 (1963).  $K_i$  values for different compounds were derived from  $IC_{50}$  values as described. Linden, J., *J. Cycl. Nucl. Res.*, **8**, 163-172 (1982).

Data from replicate experiments are tabulated as means  $\pm$  SEM.

5

*At other Adenosine Receptors:*

[<sup>3</sup>H]CPX. Bruns, R. F. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **335**, 59-63 (1987). <sup>125</sup>I-ZM241385 and <sup>125</sup>I-ABA were utilized in radioligand binding assays to membranes derived from HEK-293 cells expressing  
10 recombinant human A<sub>1</sub>, A<sub>2A</sub> and A<sub>3</sub> ARs, respectively. Binding of [<sup>3</sup>H]*R-N*<sup>6</sup>-phenylisopropyladenosine. Schwabe, U. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **313**, 179-187 (1980). ([<sup>3</sup>H]*R*-PIA, Amersham, Chicago, IL) to A<sub>1</sub> receptors from rat cerebral cortical membranes and of [<sup>3</sup>H]CGS 21680. Jarvis, M.F. *et al.*, *J. Pharmacol. Exp. Therap.*, **251**, 888-893 (1989). (Dupont NEN,  
15 Boston, MA) to A<sub>2A</sub> receptors from rat striatal membranes was performed as described. Adenosine deaminase (3 units/mL) was present during the preparation of the brain membranes, in a pre-incubation of 30 min at 30°C, and during the incubation with the radioligands. All non-radioactive compounds were initially dissolved in DMSO, and diluted with buffer to the final  
20 concentration, where the amount of DMSO never exceeded 2%. Incubations were terminated by rapid filtration over Whatman GF/B filters, using a Brandell cell harvester (Brandell, Gaithersburg, MD). The tubes were rinsed three times with 3 mL buffer each.

At least six different concentrations of competitor, spanning 3 orders of  
25 magnitude adjusted appropriately for the  $IC_{50}$  of each compound, were used.  $IC_{50}$  values, calculated with the nonlinear regression method implemented in (Graph-Pad Prism, San Diego, CA), were converted to apparent  $K_i$  values as described. Linden, J., *J. Cycl. Nucl. Res.*, **8**:163-172 (1982). Hill coefficients of the tested compounds were in the range of 0.8 to 1.1.

30

*Functional assay:*

HEK-A<sub>2B</sub> cells from one confluent T75 flask were rinsed with Ca<sup>2+</sup> and Mg<sup>2+</sup> -free Dulbecco's phosphate buffered saline (PBS) and then incubated in Ca<sup>2+</sup> and Mg<sup>2+</sup> - free HBSS with 0.05% trypsin and 0.53 mM EDTA until the  
5 cells detached. The cells were rinsed twice by centrifugation at 250 x g in PBS and resuspended in 10 mL of HBSS composed of 137 mM NaCl, 5 mM KCl, 0.9 mM MgSO<sub>4</sub>, 1.4 mM CaCl<sub>2</sub>, 3 mM NaHCO<sub>3</sub>, 0.6 mM Na<sub>2</sub>HPO<sub>4</sub>, 0.4 mM KH<sub>3</sub>PO<sub>4</sub>, 5.6 mM glucose, and 10 mM HEPES, pH 7.4 and the Ca<sup>2+</sup>-sensitive fluorescent dye indo-1-AM (5 μM) 37° for 60 min. The cells were rinsed once  
10 and resuspended in 25 mL dye-free HBSS supplemented with 1 U/ml adenosine deaminase and held at room temperature. Adenosine receptor antagonists prepared as 100X stocks in DMSO or vehicle was added and the cells and transferred to a 37° bath for 2 minutes. Then the cells (1 million in 2 ml) were transferred to a stirred cuvette maintained at 37° within an Aminco SLM 8000  
15 spectrofluorometer (SML instruments, Urbana IL). The ratios of indo-1 fluorescence obtained at 400 and 485 nm (excitation, 332 nm) was recorded using a slit width of 4 nm. NECA was added after a 100 s equilibration period.

*Cyclic AMP accumulation*

20 Cyclic AMP generation was performed in DMEM/HEPES buffer (DMEM containing 50 mM HEPES, pH 7.4, 37°C). Each well of cells was washed twice with DMEM/HEPES buffer, and then 100 μL adenosine deaminase (final concentration 10 IU/mL) and 100 μL of solutions of rolipram and cilostamide (each at a final concentration of 10 μM) were added, followed  
25 by 50 μL of the test compound (appropriate concentration) or buffer. After 15 minutes, incubation at 37°C was terminated by removing the medium and adding 200 μL of 0.1 M HCl. Acid extracts were stored at -20°C until assay. The amounts of cyclic AMP were determined following a protocol which utilized a cAMP binding protein (PKA) [van der Wenden *et al.*, 1995], with the following  
30 minor modifications. The assay buffer consisted of 150 mM K<sub>2</sub>HPO<sub>4</sub>/10 mM EDTA/ 0.2% BSA FV at pH 7.5. Samples (20 mL) were incubated for 90 minutes at 0°C. Incubates were filtered over GF/C glass microfiber filters in a Brandel M-24 Cell Harvester. The filters were additionally rinsed with 4 times

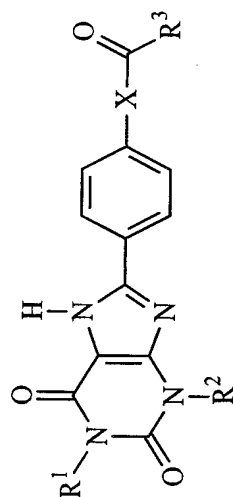
2 mL 150 mM  $K_2HPO_4$ / 10 mM EDTA (pH 7.5, 4°C). Punched filters were counted in Packard Emulsifier Safe scintillation fluid after 2 hours of extraction.

The data from the affinity testing for the compounds of the invention are reported in Tables 1, 2, 3 and 4. The data are reported as  $K_i$  in nM or

- 5 % displacement of specific binding at the designated concentration (where “r” indicates rat cell receptors and “h” indicates human cell receptors).

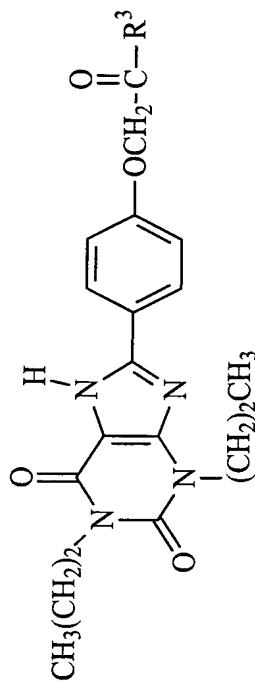
The data reported for the  $A_1$  term indicates the level of displacement of specific [ $^3H$ ]R-PIA binding in rat brain membranes ( $rA_1$ ) or recombinant human  $A_1$  receptors ( $hA_1$ ) in HEK 293 cells, expressed as  $K_i \pm S.E.M.$  ( $n = 3-5$ ). The  
10 data reported for the  $A_{2A}$  term is the level of displacement of specific [ $^3H$ ]CGS 21680 binding in rat striatal membranes ( $rA_{2A}$ ) or recombinant human  $A_{2A}$  receptors ( $hA_{2A}$ ) in HEK 293 cells, expressed as  $K_i \pm S.E.M.$  ( $n = 3-5$ ). The data reported for the  $A_{2B}$  term is the level of displacement of specific [ $^{125}I$ ]ABOPX binding at human  $A_{2B}$  receptors ( $hA_{2B}$ ) expressed in HEK-293 cells, expressed as  
15  $K_i \pm S.E.M.$  ( $n = 3-4$ ). The  $A_3$  term is the level of displacement of specific [ $^{125}I$ ]ABA binding at human  $A_3$  receptors ( $hA_3$ ) expressed in HEK-293 cells, in membranes, expressed as  $K_i \pm S.E.M.$  ( $n = 3-4$ ).

In Table 4 the data reported for the  $A_{2A}$  term is the level of displacement of specific [ $^3H$ ]CGS 21680 binding to rat striatal membranes ( $rA_{2A}$ ) or  
20 [ $^{125}I$ ]ABOPX binding to recombinant human  $A_{2B}$  receptors ( $hA_{2B}$ ) in HEK 293 cells, expressed as  $K_i \pm S.E.M.$  in  $\mu M$  ( $n = 3-6$ ) or as a percentage of specific binding displaced by a solution of test compound, at the the designated concentration. In Table 4 the data reported for the  $hA_3$  term is the level of displacement of specific [ $^{125}I$ ]AB-MECA binding at human  $A_3$  receptors  
25 expressed in HEK-293 cells, in membranes, expressed as  $K_i \pm S.E.M.$  in  $\mu M$  ( $n = 3-4$ ).

Table 1. Affinities or antagonistic activities of xanthine derivatives in radioligand binding assays at A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors.

Compound	R <sup>1</sup> , R <sup>2</sup>	X	R <sup>3</sup>	rA <sub>1</sub>	rA <sub>2A</sub>	K <sub>i</sub> or IC <sub>50</sub> (nM)	hA <sub>2B</sub>	hA <sub>3</sub>	hA <sub>1</sub> /hA <sub>2B</sub>	hA <sub>2A</sub> /hA <sub>2B</sub>	hA <sub>3</sub> /hA <sub>2B</sub>
4a	n-Pr	OCH <sub>2</sub>	OH	58	2,200	175 ± 57(h)	40 ± 4	3,910 ± 2,140	4.4	15	98
4b	n-Pr	OCH <sub>2</sub>	O-Succinimide	153	595 ± 128(h)	127	9.75 ± 4.80	75,700 ± 6,500(r)	227		
4c	n-Pr	OCH <sub>2</sub>	NHN- dimethylmaleyl NH(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	11.1 ± 2.4	126 ± 41	1,970 ± 550(h)	26.6 ± 4.0	670 ± 154	110	74	25
4d	n-Pr	OCH <sub>2</sub>	OH	6.82 ± 1.57(h)	18.4 ± 0.03(h)	63	7.75 ± 0.14	25.6 ± 5.0	0.9	2.4	3.3
5	allyl	OCH <sub>2</sub>	OH	756 ± 147	4,290 ± 570	2,370 ± 290(h)	141 ± 29(h)	816 ± 91	12	17	5.8
6	n-butyl	OCH <sub>2</sub>	OH	43.1 ± 9.9	874 ± 107	2,540 ± 1,250(h)	48.0 ± 16.9	90.3 ± 14.2	3.1	53	1.9
7	Bn	OCH <sub>2</sub>	OH	149 ± 83(h)	2,540 ± 1,250(h)	25 ± 3% (100,000 nM) <sup>a</sup>	1,760 ± 110	27,500 ± 2,500(r)			
8	n-Pr	CH=CH	OH	15	800	190 ± 71 (h)	60 ± 2	30 ± 14	2.3	3.2	0.5
9	c-HexylCH <sub>2</sub>	CH=CH	OH	602 ± 24	< 10% (10,000nM) <sup>a</sup>	1,518 ± 980(h)	199 ± 52	15,000 ± 1,700(r)	25	7.6	4.6
10	Bn	CH=CH	OH	4,890 ± 530(h)	4,450 ± 1,230	201 ± 23	469 ± 23	922 ± 399			
71	CH-CH=CH <sub>2</sub>	OCH <sub>2</sub>	NH-Ph(4-CN)	61,200 ± 43,000	4,230 ± 340	9.53 ± 1.9	2680 ± 1810				

a) % Displacement of specific binding at the designated concentration of test compound.

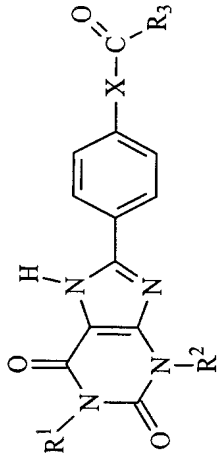
Table 2. Affinities or antagonistic activities of xanthine amide derivatives in radioligand binding assays<sup>a</sup> at A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors.

Compound	R <sup>3</sup>	K <sub>i</sub> or IC <sub>50</sub> (nM)									
		τA <sub>1</sub>	τA <sub>2A</sub>	hA <sub>1</sub>	hA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	hA <sub>3</sub> /hA <sub>2B</sub>	hA <sub>1</sub> /hA <sub>2B</sub>	hA <sub>2A</sub> /hA <sub>2B</sub>	
11	NH <sub>2</sub>	20.0 ± 3.8	76.3 ± 14.0			16.3 ± 4.2					
12	NH-Ph	4.22 ± 0.88	45.6 ± 1.4	40.1 ± 5.1	25.8 ± 4.5	1.48 ± 0.63	137 ± 54	27	17	93	
13	NH-CH <sub>2</sub> Ph	5.02 ± 0.55	25.9 ± 7.6	54.7 ± 21.2	23.8 ± 5.71	2.04 ± 0.17	79.2 ± 17.8	27	12	39	
14	NH-CH(Ph) <sub>2</sub>	120 ± 21	20 ± 8% (1000) <sup>b</sup>			33.7 ± 17.0					
15	N(CH <sub>2</sub> Ph) <sub>2</sub>	167 ± 49	2,750 ± 800	690 ± 98	642 ± 198	9.88 ± 1.05	284 ± 14	70	65	29	
16	N(CH <sub>3</sub> )Ph	218 ± 80	497 ± 250			5.42 ± 1.71					
17	N(CH <sub>2</sub> COOEt) <sub>2</sub>	26.8 ± 2.4	999 ± 144			43.4 ± 8.4					
18	NH-Ph-(2-COCH <sub>3</sub> )	27.9 ± 1.6	434 ± 129	335 ± 64	431 ± 176	2.74 ± 1.01	61.9 ± 3.4	120	160	23	
19	NH-Ph-(3-COCH <sub>3</sub> )	439 ± 111	949 ± 394	234 ± 28	58.9 ± 7.1	4.92 ± 0.55	352 ± 69	48	12	72	
20	NH-Ph-(4-COCH <sub>3</sub> )	37.6 ± 4.0	548 ± 183	157 ± 8	112 ± 37	1.39 ± 0.30	230 ± 23	110	81	170	
21	NH-Ph-(4-COOCH <sub>3</sub> )	38.4 ± 3.9	541 ± 128	225 ± 9	3,100 ± 1540	3.93 ± 1.35	363 ± 148	57	790	92	
22	NH-Ph-(4-CONH <sub>2</sub> )	10.2 ± 2.5	683 ± 167			7.75 ± 1.11					
23	NH-Ph-(4-CONHCH <sub>3</sub> )	24.8 ± 1.8	98.1 ± 49.6			3.34 ± 0.51					
24	NH-Ph-(4-COOH)	145 ± 28	220 ± 79			16.1 ± 4.7					

Compound	R <sup>3</sup>	K <sub>i</sub> or IC <sub>50</sub> (nM)									
		rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>1</sub>	hA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	hA <sub>3</sub> /hA <sub>2B</sub>	hA <sub>1</sub> /hA <sub>2B</sub>	hA <sub>2A</sub> /hA <sub>2B</sub>	
25	NH-Ph-(4-CH <sub>3</sub> )	17.5 ± 5.0	126 ± 38			1.88 ± 0.76					
26	NH-Ph-(4-OH)	5.88 ± 1.06	63.3 ± 20.4			3.71 ± 0.76					
27	NH-Ph-(4-CN)	16.8 ± 3.6	612 ± 287	403 ± 194	503 ± 10.8	1.97 ± 0.31	570 ± 184	210	260	290	
28	NH-Ph-(4-NO <sub>2</sub> )	13.1 ± 3.9	1,180 ± 360	57.0 ± 3.1	70.0 ± 10.7	1.52 ± 0.24	138 ± 17.1	38	46	91	
29	NH-Ph-(4-CF <sub>3</sub> )	44.6 ± 6.5	917 ± 258	61.2 ± 8.2	238 ± 28	2.14 ± 0.47	213 ± 94	29	110	100	
30	NH-Ph-(4-F)	2.72 ± 0.51	988 ± 518	17.9 ± 4.5	16.6 ± 3.6	2.22 ± 0.19	391 ± 147	8.1	7.5	176	
31	NH-Ph-(4-Cl)	6.35 ± 1.47	995 ± 550	49.7 ± 14.2	187 ± 38	2.47 ± 0.71	1,870 ± 370	20	400	760	
32	NH-Ph-(4-Br)	7.46 ± 2.66	221 ± 36	73.5 ± 23.3	1,640 ± 660	2.35 ± 0.01	2,300 ± 420	31	700	980	
33	NH-Ph-(4-I)	15.7 ± 4.2	152 ± 47	293 ± 67	5,140 ± 540	2.13 ± 0.12	1,270 ± 130	140	2,400	600	

a) The methods of each binding assay are described above.

Table 3. Affinities or antagonistic activities of miscellaneous xanthine derivatives in radioligand binding assays<sup>a</sup> at A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors.

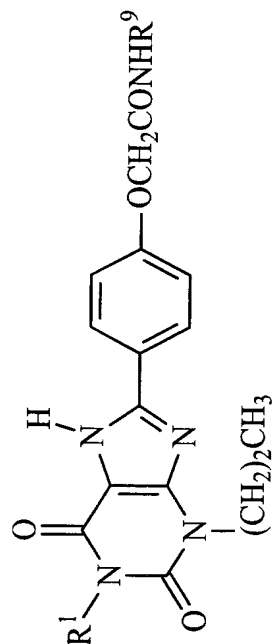


K<sub>i</sub> or IC<sub>50</sub> (nM)

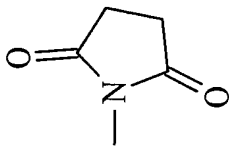
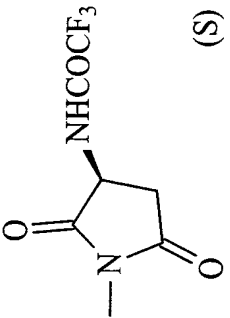
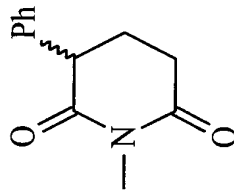
Compound	R <sup>1</sup> , R <sup>2</sup>	X	R <sup>3</sup>	rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>
34	n-Pr	CH=CH	NHN-dimethylmalelyl	3.94 ± 1.20	406 ± 105	16.7 ± 3.0	31.0 ± 3.1
35	n-Pr	CH=CH	NH-Ph-(2-COCH <sub>3</sub> )	105 ± 5(h) 7.67 ± 2.20	223 ± 55 (h) 143 ± 50	3.65 ± 0.98	121 ± 138
36	c- HexMe	CH=CH	NH-Ph-(2-COCH <sub>3</sub> )	(10,000 nM) <sup>b</sup>	(10,000 nM) <sup>b</sup>	(10,000 nM) <sup>b</sup>	
37	Bn	CH=CH	NH-Ph-(2-COCH <sub>3</sub> )	34,300	(10,000 nM) <sup>b</sup>	(10,000 nM) <sup>b</sup>	
38	Bn	OCH <sub>2</sub>	NH-Ph-(2-COCH <sub>3</sub> )	(10,000 nM) <sup>b</sup>	(10,000 nM) <sup>b</sup>	(10,000 nM) <sup>b</sup>	
39	Et	OCH <sub>2</sub>	NH-Ph-(4-CH <sub>3</sub> )	34.9 ± 0.3	71.1 ± 7.7	1.78 ± 0.43	(1000 nM) <sup>b</sup>
40	Et	OCH <sub>2</sub>	NH-Ph- (4-CH <sub>2</sub> CONH- (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub> )	65.0 ± 15.4	1370 ± 490	15.2 ± 6.8	

a) The methods of each binding assay are as described above.  
b) <10% displacement of specific binding at the the designated concentration of test compound.

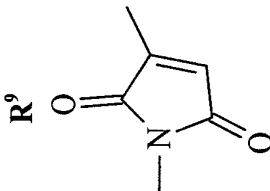
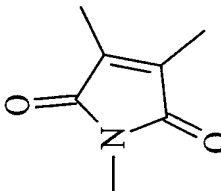
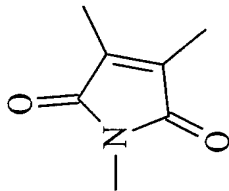


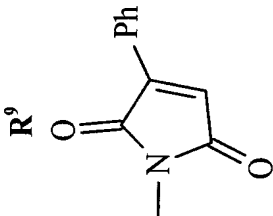
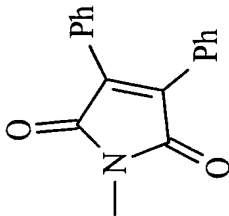
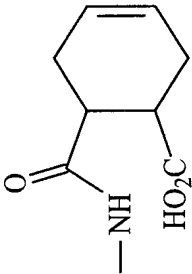
Table 4. Affinities of xanthine derivatives in radioligand binding assays<sup>b</sup> at rat A<sub>1</sub>, rat A<sub>2A</sub>, human A<sub>2B</sub>, and human A<sub>3</sub> receptors, unless noted<sup>a</sup>.

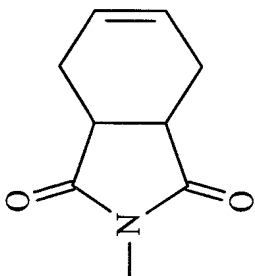
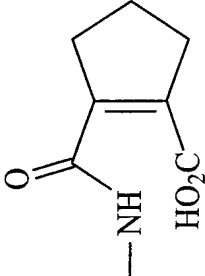
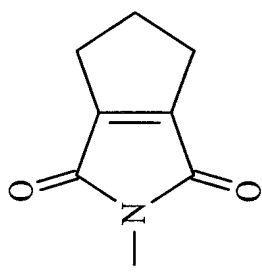
Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
4e	—	Pr	51.6 ± 8.0, 230 ± 59 (h) <sup>a</sup>	128 ± 15, 342 ± 10 (h) <sup>a</sup>	18.7 ± 0.5, 34.5 ± 6.3 <sup>a</sup>	48.5 ± 0.8 <sup>a</sup>	2.8
4f	—NH <sub>2</sub>	Pr	16.0 ± 0.5	63.8 ± 21.3	13.2 ± 5.9	498 ± 139	1.2
41	—NH-COCH <sub>3</sub>	Pr	6.51 ± 1.24, 125 ± 14 (h) <sup>a</sup>	227 ± 64, 186 ± 9 (h) <sup>a</sup>	65.4 ± 6.5, 33.8 ± 13.7 <sup>a</sup>	30.9 ± 8.2 <sup>a</sup>	0.10
42		Pr	73.3 ± 22.0, 219 ± 3 (h) <sup>a</sup>	174 ± 32, 795 ± 98 (h) <sup>a</sup>	116 ± 10, 97.8 ± 3.3 <sup>a</sup>	173 ± 27	1.6

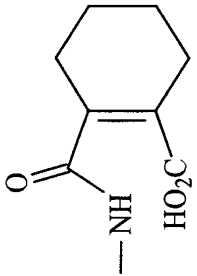
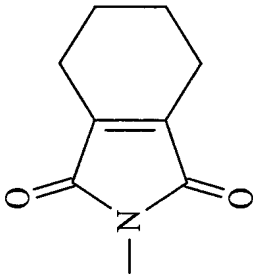
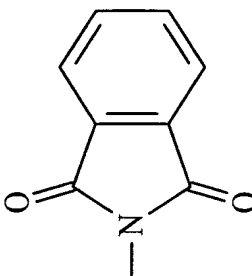
Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
43		Pr	55.9 ± 25.1	805 ± 44	18.6 ± 6.1	766 ± 176	3.0
			75.2 ± 5.5 (h) <sup>a</sup>	27.2 ± 8.6 (h) <sup>a</sup>			
44		Pr	74.3 ± 6.6	139 ± 32	30.2 ± 0.5	1560	2.5
45		Pr	3.87 ± 1.20	21.4 ± 6.1	3.86 ± 0.7	151 ± 99	1.0

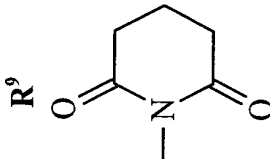
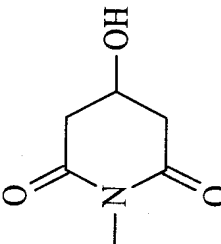
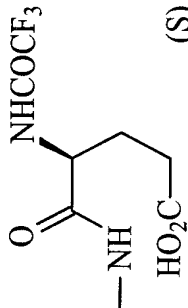
(S)

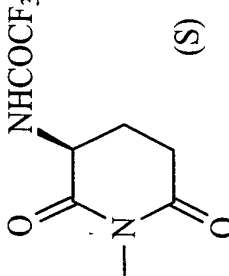
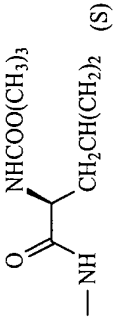
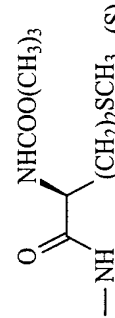
Compound	$R^9$	$R^1$	Ki (nM) or % displacement				
			$rA_1$	$rA_{2A}$	$hA_{2B}$	$hA_3$	$rA_1/hA_{2B}$
46		Pr	203 ± 41	1230 ± 270	144 ± 11	551 ± 106	1.4
47		Pr	11.1 ± 2.4, 3030 ± 1110 (h) <sup>a</sup>	126 ± 41, 1970 ± 550 (h) <sup>a</sup>	19.4 ± 6.2, 33.8 ± 1.9 <sup>a</sup>	670 ± 154 <sup>a</sup>	0.57
48		H	3590 ± 920, 8080 ± 720 (h) <sup>a</sup>	36 ± 4%, (100,000 nM) <sup>c</sup> , 5480 ± 920 (h) <sup>a</sup>	1800 ± 0, 1900 ± 280 <sup>a</sup>	14,200 ± 11,500 <sup>a</sup>	2.0

Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
49		Pr	225 ± 76	1540 ± 280	66.7 ± 37.0	748 ± 234	3.4
50		Pr	95.8 ± 25.1	2100 ± 630	27.9 ± 8.5	3450 ± 1470	3.4
51		Pr	134 ± 19	813 ± 299	51.0 ± 7.0	1060 ± 150	2.6

Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
52		Pr	36.4 ± 6.2	689 ± 477	10.0 ± 3.0	370 ± 190	3.6
			129 ± 20 (h) <sup>a</sup>	301 ± 31 (h) <sup>a</sup>			
53		Pr	81.7 ± 31.2	708 ± 169	78.5 ± 20.5	1180 ± 700	1.0
54		Pr	41.3 ± 6.4	1160 ± 337	21.5 ± 1.5	309 ± 88	1.9

Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
55		Pr	47.2 ± 6.8	422 ± 136	17.3 ± 6.3	438 ± 109	2.7
			145 ± 11 (h) <sup>a</sup>	95.6 ± 16.8 (h) <sup>a</sup>			
56		Pr	61.9 ± 11.3	415 ± 157	35.8 ± 0.7	245 ± 45	1.7
57		Pr	26.3 ± 2.3,	392 ± 117,	64.4 ± 0.8,	147 ± 21 <sup>a</sup>	0.41
			210 ± 42 (h) <sup>a</sup>	359 ± 21 (h) <sup>a</sup>	46.4 ± 14.5 <sup>a</sup>		

Compound	R <sup>9</sup>	R <sup>1</sup>	Ki (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
58		Pr	14.0 ± 2.3	135 ± 39	22.0 ± 5.5	200 ± 45	0.6
59		Pr	41.2 ± 16.6	164 ± 61	25.7 ± 5.5	290 ± 88	1.6
60		Pr	70.8 ± 30.9	872 ± 412	24.8 ± 7.3	430 ± 44	2.9

Compound	R <sup>9</sup>	R <sup>1</sup>	K <sub>i</sub> (nM) or % displacement				
			rA <sub>1</sub>	rA <sub>2A</sub>	hA <sub>2B</sub>	hA <sub>3</sub>	rA <sub>1</sub> /hA <sub>2B</sub>
61	 (S)	Pr	53.5 ± 6.5	440 ± 106	13.0 ± 3.5	726 ± 245	4.1
			149 ± 6 (h) <sup>a</sup>	178 ± 20 (h) <sup>a</sup>			
62	 (S)	Pr	197 ± 67	2750 ± 950	47.5 ± 2.5	195 ± 84	4.1
63	 (S)	Pr	113 ± 27	524 ± 285	39.7 ± 13.6	690 ± 570	2.8
64	Cbz-(Gly) <sub>2</sub> -NH-	Pr	36.0 ± 6.6	609 ± 95	10.8 ± 5.0	323 ± 47	3.3
			200 ± 22 (h) <sup>a</sup>	830 ± 84 (h) <sup>a</sup>			

a) K<sub>i</sub> values were determined in radioligand binding assays at recombinant human A<sub>1</sub> and A<sub>2A</sub> receptors expressed in HEK-293 cells vs [<sup>3</sup>H]CPX and [<sup>125</sup>I]ZM241385, respectively. Affinity of xanthine derivatives at human A<sub>2B</sub> receptors expressed in HEK-293 cells was determined using [<sup>125</sup>I]-ABOPX. Affinity at recombinant human A<sub>3</sub> receptors expressed in HEK-293 cells was determined using [<sup>125</sup>I]ABA.

b) The methods of each binding assay are as described above.

c) % Displacement of specific binding at the the designated concentration of test compound.



The potency of the xanthine derivatives at human  $A_{2B}$  receptors was evaluated using two binding assays. Tables 1, 2 and 3 illustrate the results from the anilide compounds. Table 4 illustrates the results from the hydrazide compounds. Figure 2 shows functional inhibition by anilide compounds. The  $K_i$  values of the xanthine derivatives were determined in displacement of binding of two non-selective radioligands 4-(2-[7-amino-2-furyl]{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl)-phenol ( $[^3H]$ ZM241385), and  $^{125}I$ -3-(4-amino-3-iodobenzyl)-8-phenyloxyacetate-1-propyl-xanthine ( $^{125}I$ -ABOPX), at human  $A_{2B}$  receptors stably expressed in HEK-293 cell membranes. The results obtained with these two radioligands were nearly identical. In order to determine selectivity, the xanthines were evaluated using standard binding assays at  $A_1$ ,  $A_{2A}$ , and  $A_3$  receptors. The initial screening utilized rat brain  $A_1/A_{2A}$  receptors (with radioligands  $[^3H]$ R-PIA and  $[^3H]$ CGS21680), and selected compounds were examined at the recombinant human subtypes, using  $[^3H]$ 8-cyclopentyl-1,3-dipropylxanthine ( $[^3H]$ CPX) ( $A_1$ , See Bruns, R.F., *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1987**, 335, 59-63.) and  $^{125}I$ -4-(2-[7-amino-2-[2-furyl]-[1,2,4]triazolo[2,3-a][1,3,5]-triazin-5-yl-amino]-ethyl)phenol ( $^{125}I$ -ZM241385) ( $A_{2A}$ ). Affinity at cloned human  $A_3$  receptors expressed in HEK-293 cells was determined using  $N^6$ -(4-amino-3- $[^{125}I]$ iodobenzyl)-adenosine ( $^{125}I$ -ABA) or  $N^6$ -(4-amino-3-iodobenzyl)-adenosine-5'-*N*-methyluronamide ( $^{125}I$ -AB-MECA).

The 8-(4-Phenylacrylic) acid derivatives, **8** - **10**, tended to be more potent at  $A_1$  receptors and less potent at  $A_{2B}$  receptors than the 8-(4-carboxymethyloxyphenyl) derivatives. The 1,3-dicyclohexylmethyl derivative, **9**, for example, was more selective for  $A_{2B}$  receptors. A primary carboxamide, **11**, was more potent than the carboxylic acid, **4a**, at  $A_1$  (3-fold) and  $A_{2A}$  (29-fold) receptors, and equipotent at  $A_{2B}$  receptors.

The adenosine receptor affinities of aryl, compounds **12** and **18** - **33**, alkyl, compound **17**, and aralkyl, compounds **13** - **16**, amides of **4a** were compared. A benzyl amide, compound **13**, and simple anilides had the highest affinity of binding, in the nanomolar range, to human  $A_{2B}$  receptors. Selectivities for the human  $A_{2B}$  versus rat  $A_1$  receptors ranged from 1- (compound **30**) to 27- (compound **20**) fold, while comparisons within the same species (human)

generally led to greater selectivities. Anilides substituted in the *p*-position with groups such as nitro, cyano, and acetyl, displayed the highest selectivity. An N-methyl anilide of **4a**, compound **16**, was 40- and 92-fold selective for human  $A_{2B}$  receptors versus rat  $A_1/A_{2A}$  receptors, thus the N-methylation reduced  
5 affinity by 3.7-fold but increased selectivity. An *o*-substituted acetophenone, compound **18** was 120-, 160-, and 23-fold selective for human  $A_{2B}$  receptors versus human  $A_1/A_{2A}/A_3$  receptors and 10-, and 160-fold selective versus rat  $A_1/A_{2A}$  receptors. The *p*-substituted acetophenone, compound **20**, was more potent at  $A_{2B}$  receptors than the corresponding *o*- and *m*- isomers. Other  
10 highly potent and moderately selective  $A_{2B}$  antagonists were a *p*-trifluoromethyl derivative, compound **29** ( $K_i$  value 2.14 nM), and a *p*-cyanoanilide, compound **27** ( $K_i$  value 1.97 nM), which was highly selective versus the other human subtypes, but only 8.5-fold selective versus rat  $A_1$  receptors. The *p*-cyanoanilide, **27**, was tritiated on the 1,3-dipropyl groups and  
15 serves as a selective radio ligand for  $A_{2B}$  receptors. A *p*-nitro derivative, compound **28**, bound to human  $A_{2B}$  receptors with a  $K_i$  of 1.52 nM but was only 35-fold selective versus human  $A_1$  receptors. A *p*-iodo derivative, compound **33** ( $K_i$  value 2.13 nM), was 140-, 2400-, and 600-fold selective for human  $A_{2B}$  receptors versus human  $A_1/A_{2A}/A_3$  receptors. Substitution of the  
20 1,3-dipropyl groups with ethyl, as in compounds **40** and **41**, offered no disadvantage for selectivity, but high affinities were maintained.

The functional effects of several selective  $A_{2B}$  antagonists in inhibiting the effects of NECA in HEK- $A_{2B}$  cells were examined (Figure 2). Several selective  $A_{2B}$  adenosine receptor antagonists at 100 nM nearly completely  
25 inhibited NECA-stimulated calcium mobilization. In comparison, XAC (8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine), which has a  $K_i$  value of 12.3 nM in binding to human  $A_{2B}$ , (See de Zwart, M.; *et al.*, *Nucleos. Nucleot.* **1998**, *17*, 969-986.) inhibited the NECA-stimulated calcium mobilization effect by about half. Thus, the potency of the xanthines  
30 in the functional assay was parallel to results from the binding assay.

The 1,2-dimethylmaleimide derivative, **47**, bound to human  $A_{2B}$  receptors with a  $K_i$  of 19 nM and proved to be selective vs. human  $A_1/A_{2A}/A_3$  receptors by 160-, 100-, and 35-fold, respectively. Other potent and selective  $A_{2B}$

antagonists were a tetrahydrophthaloyl derivative **52** ( $K_i$  value 10 nM) and amino acid conjugates of the XCC-hydrazide, *i.e.*, the glutarimide **61** ( $K_i$  value 13 nM) and protected dipeptide **64** ( $K_i$  value 11 nM). Compound **55** displayed a  $K_i$  value of 17 nM. Other derivatives displaying selectivity for  $A_{2B}$  receptors, but with less potency ( $K_i$  values in nM) were compounds: **44** (30), **49** (67), **50** (28), **60** (25), **62** (48), and **63** (40).

### Synthesis and Characterization

Compounds **4a**, **4b**, **4c**, **11**, **25**, and **26** were synthesized as reported in Jacobson, *et al.*, *J. Med. Chem.* **1985**, 28, 1334-1340. Compound **5**, **6**, **7** and **10** were synthesized as reported in Kim, H. O.; *et al.*, *J. Med. Chem.* **1994**, 37, 3373-3382. Compound **39** and **40** were synthesized as reported in Jacobson, K. A *et al.*, *J. Med. Chem.* **1987**, 30, 211-214. *R*-PIA, NECA, XAC, and 2-chloroadenosine were purchased from Research Biochemicals International (Natick, MA). All other agents were purchased from Aldrich (St. Louis, MO).

Proton nuclear magnetic resonance spectroscopy was performed on a Varian GEMINI-300 spectrometer and spectra were taken in DMSO- $d_6$  or  $CDCl_3$ . Unless noted, chemical shifts are expressed as ppm downfield from tetramethylsilane or relative ppm from DMSO (2.5 ppm). Chemical-ionization (CI) mass spectrometry was performed with a Finnigan 4600 mass spectrometer, and Electron-impact (EI) mass spectrometry with a VG7070F mass spectrometer at 6 kV for high resolution mass. FAB (fast atom bombardment) mass spectrometry was performed with a JEOL SX102 spectrometer using 6-kV Xe atoms.

Elemental analysis ( $\pm 0.4\%$  acceptable) was performed by Atlantic Microlab Inc. (Norcross, GA). All melting points were determined with a Unimelt capillary melting point apparatus (Arthur H. Thomas Co., PA) and were uncorrected. All xanthine derivatives were homogeneous as judged using TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). All xanthine derivatives tested in binding assays were shown to be homogeneous by TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). NMR and mass spectra were shown to be consistent with the assigned structure.

**Example 1. General procedure for the preparation of amide derivatives of 8-[4-[[[carboxyl]methyl]oxy]phenyl]-1,3-dipropylxanthine analogs 4a, 7-10 (collectively "XCC")**

**Method A (Carbodiimide)**

5           A solution of XCC (0.0517 mmole), the desired amine compound (0.103 mmole), EDAC (20 mg, 0.103 mmole), and DMAP (4 mg, 0.032 mmole) in 2 mL of anhydrous DMF/CH<sub>2</sub>Cl<sub>2</sub> (1:1 v/v) was stirred at room temperature for 24 hours. The mixture was evaporated to dryness under reduced pressure. The residue was purified by preparative silica gel TLC  
10 (CHCl<sub>3</sub>:MeOH=20:1) and crystallization in MeOH/ether or MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford the desired compounds (12-14, 18, 36).

**Method B (BOP-Cl)**

          A solution of XCC (0.0517 mmole), the desired amine compound  
15 (0.103 mmole), BOP-Cl (14 mg, 0.0517 mmole), and triethylamine (20 µl, 0.206 mmole) in 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 24 hours. The mixture was treated according to the same procedure as Method A for purification of the desired compounds. (15, 17, 19, 20, 38)

20 **Method C (Acid Chloride)**

          A solution of XCC (0.0517 mmole) in 1 mL of thionyl chloride was stirred at 70°C for 4 hours. The excess thionyl chloride was removed with a nitrogen stream. To the residue was added a solution of the desired amine compound (0.103 mmole) in 1 mL of anhydrous pyridine and 1 mL of  
25 anhydrous CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at room temperature for 24 hours. The mixture was subjected to the same procedure as described in Method A for purification of the desired compounds. (16, 21, 22, 27-35, 37)

**Example 2. General procedure for the preparation of xanthine hydrazide derivatives**

The hydrazide of XCC, **4f**, was acylated with a variety of mono- and dicarboxylic acids. Cyclization reactions were carried out for dicarboxylic acids, in two steps using an anhydride, (compound **72**, Figure 4), for acylation, leading to imide (5- or 6-membered ring) derivatives. The final step of ring-closure of **73** to **74** was effected at 50 °C, using excess carbodiimide and 1-hydroxybenzotriazole as catalyst. In some cases, where symmetric dicarboxylic acids were used, it was possible to isolate both the open structure, **73**, and the cyclized imide form, **74**. Pairs of open and cyclized derivatives of symmetric dicarboxylic acids prepared include compounds **51** - **56**. Also, the glutamic acid derivative **60**, was prepared using orthogonal protecting and the corresponding imide, **61**. An 8-phenyl analogue, **48**, of enprofylline was synthesized by standard methods from the asymmetric urea, (Figure 5).

**A. Carboxyalkyl amide derivatives**

A mixture of compound **4f** (10 mg, 0.025 mmol), and 2 equivalents of anhydride were stirred in 1 mL of DMF for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC (CHCl<sub>3</sub>:MeOH=10:1) to afford the corresponding carboxyalkylamide derivative as a white solid with 40-70% yield. (compounds **41**, **42**, **51**, **53**, **55**)

**B. Cyclic imide derivatives**

A mixture of compound **4f** (10 mg, 0.025 mmol), 1.5-2.0 equivalents of anhydride and 1 equivalent of DIPEA were stirred in 1 mL of DMF at room temperature. When the starting material **4f** disappeared, as judged by TLC, a mixture of 2-3 equivalents of HOBt, EDAC, and DIPEA, dissolved in 0.5 mL of DMF, was added. The mixture was stirred at room temperature or at 50°C for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC (CHCl<sub>3</sub>:MeOH=10:1) to afford the cyclic imide derivative as a white solid, 40-70% yield. (compounds **43**, **44**, **45**, **46**, **47**, **48**, **49**, **50**, **52**, **54**, **56**, **57**, **58**, and **59**)

**C. Coupling with activated N-protected amino acids**

A mixture of compound **4f** (10 mg, 0.025 mmol), 1.5-2.0 equivalents of activated (hydroxy- succinimide or 4-nitrophenyl ester) N-protected amino acid and 1 equivalent of DIPEA and DMAP, in 1 mL of DMF, was stirred at 25-50°C for 8-24 hours. The reaction mixture was concentrated to dryness. The residue was purified by preparative TLC (CHCl<sub>3</sub>:MeOH=10:1) to afford the product as a white solid, 40-70% yield. (compounds **62**, **63** and **64**)

**Example 3. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-dibenzyl-xanthine (7)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 4.23 (s, 2H, -OCH<sub>2</sub>-), 5.10 (s, 2H, -NCH<sub>2</sub>-), 5.23 (s, 2H, -NCH<sub>2</sub>-), 6.88 (d, 2H, *J* = 8.8 Hz, Ar), 7.22-7.41 (m, 10H, 2x-Ph), 8.01 (d, 2H, *J* = 8.8 Hz, Ar).

**Example 4. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-dibenzyl-xanthine**

**(10)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 5.12 (s, 2H, -NCH<sub>2</sub>-), 5.26 (s, 2H, -NCH<sub>2</sub>-), 6.63 (d, 1H, *J* = 15.6 Hz, -CH=), 7.22-7.43 (m, 10H, 2x-Ph), 7.63 (d, 1H, *J* = 15.6 Hz, -CH=), 7.84 (d, 2H, *J* = 8.8 Hz, Ar), 8.17 (d, 2H, *J* = 8.8 Hz, Ar).

**Example 5. 8-[4-[(Phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (12)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.80 (s, 2H, -OCH<sub>2</sub>-), 7.06-7.12 (m, 1H, -Ph), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.33 (t, 2H, *J* = 7.8 Hz, -Ph), 7.64 (d, 2H, *J* = 7.8 Hz, -Ph), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.13 (s, 1H, -NH).

**Example 6. 8-[4-[(Benzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (13)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.36 (d, 2H, *J* = 5.9 Hz, -NH-CH<sub>2</sub>-), 4.80 (s, 2H, -OCH<sub>2</sub>-), 7.12 (d, 2H, *J* = 8.8 Hz, Ar),

7.22-7.34 (m, 5H, -Ph), 8.08 (d, 2H,  $J = 8.8$  Hz, Ar), 8.70 (t, 1H,  $J = 5.9$  Hz, -NH-).

**Example 7. 8-[4-[(Diphenylmethylcarbamoylmethyl)oxy]phenyl]-1,3-di-**  
5 **(n-propyl)xanthine (14)**

$^1\text{H}$  NMR (DMSO- $d_6$ ). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
(2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.73 (s, 2H,  
-OCH<sub>2</sub>-), 6.20 (d, 1H,  $J = 8.8$  Hz, -NH-CH<sub>2</sub>-), 7.08 (d, 2H,  $J = 8.8$  Hz, Ar),  
7.23-7.37 (m, 10H, 2x-Ph), 8.07 (d, 2H,  $J = 8.8$  Hz, Ar), 9.06 (d, 1H,  $J = 8.8$   
10 Hz, -NH-).

**Example 8. 8-[4-[(Dibenzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-**  
**propyl)xanthine (15)**

$^1\text{H}$  NMR (DMSO- $d_6$ ). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
15 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.52 (s, 2H,  
-NCH<sub>2</sub>-), 4.59 (s, 2H, -NCH<sub>2</sub>-), 5.03 (s, 2H, -OCH<sub>2</sub>-), 6.99 (d, 2H,  $J = 8.8$  Hz,  
Ar), 7.22-7.44 (m, 10H, 2x-Ph), 8.05 (d, 2H,  $J = 8.8$  Hz, Ar).

**Example 9. 8-[4-[(N-Methyl-N-phenylcarbamoylmethyl)oxy]phenyl]-1,3-**  
20 **di-(n-propyl)xanthine (16)**

$^1\text{H}$  NMR (DMSO- $d_6$ ). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
(2m, 4H, 2x-CH<sub>2</sub>-), 3.22 (s, 3H, -NCH<sub>3</sub>), 3.88 and 4.01 (2t, 4H,  $J = 6.8$  Hz, 2x-  
NCH<sub>2</sub>-), 4.54 (s, 2H, -OCH<sub>2</sub>-), 6.91 (bs, 2H, Ar), 7.30-7.55 (m, 5H, -Ph), 8.03  
(d, 2H,  $J = 8.8$  Hz, Ar).

25

**Example 10. 8-[4-[(N,N-bis(ethoxycarbonylmethyl) carbamoylmethyl)-**  
**oxy]phenyl]-1,3-di-(n-propyl)xanthine (17)**

$^1\text{H}$  NMR (DMSO- $d_6$ ). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.20 (2t, 6H,  $J$   
 $= 6.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J$   
30  $= 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.06-4.20 (m, 4H, -OCH<sub>2</sub>-), 4.11 (s, 2H, -NCH<sub>2</sub>-), 4.38  
(s, 2H, -NCH<sub>2</sub>-), 4.94 (s, 2H, -OCH<sub>2</sub>-), 7.00 (d, 2H,  $J = 8.8$  Hz, Ar), 8.05 (d,  
2H,  $J = 8.8$  Hz, Ar).

**Example 11. 8-[4-(((2-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (18)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.70 (s, 3H, -COCH<sub>3</sub>), 4.72 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.56 (t, 1H, *J* = 6.8 Hz, Ar), 7.69 (t, 1H, *J* = 6.8 Hz, Ar), 8.02 (d, 2H, *J* = 6.8 Hz, Ar), 8.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.48 (m, 1H, -NH-).

**Example 12. 8-[4-(((3-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (19)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 2.57 (s, 3H, -COCH<sub>3</sub>), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.82 (s, 2H, -OCH<sub>2</sub>-), 7.16 (d, 2H, *J* = 8.8 Hz, Ar), 7.50 (t, 1H, *J* = 7.8 Hz, Ar), 7.71 (d, 1H, *J* = 7.8 Hz, Ar), 7.92 (d, 1H, *J* = 7.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar), 8.24 (s, 1H, Ar), 10.36 (s, 1H, -NH-).

**Example 13. 8-[4-(((4-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (20)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 2.54 (s, 3H, -COCH<sub>3</sub>), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.79 (d, 2H, *J* = 7.8 Hz, Ar), 7.96 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.48 (s, 1H, -NH-).

**Example 14. 8-[4-(((4-Methoxycarbonyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (21)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.83 (s, 3H, -OCH<sub>3</sub>), 3.86 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.79 (d, 2H, *J* = 7.8 Hz, Ar), 7.96 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.50 (s, 1H, -NH-).



**Example 15. 8-[4-(((4-Carbamoyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (22)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.82 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.26 (bs, 1H, -NH<sub>2</sub>), 7.70 (d, 2H, *J* = 7.8 Hz, Ar), 7.85 (m, 3H, Ar and -NH<sub>2</sub>), 8.10 (d, 2H, *J* = 8.8 Hz, Ar), 10.35 (s, 1H, -NH-).

**Example 16. 8-[4-(((4-Methylcarbamoyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (23)**

A solution of 20 mg of compound **21** (0.0358 mmole) in 1 mL of 40% aqueous methylamine was stirred at room temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure, and the residue was purified by preparative silica gel TLC (CHCl<sub>3</sub>:MeOH=20:1) and re-crystallized in MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 9 mg of compound **23**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 2.76 (s, 3H, -NHCH<sub>3</sub>), 3.86 and 4.01 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.82 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.71 (d, 2H, *J* = 7.8 Hz, Ar), 7.81 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 8.33 (m, 1H, -NHCH<sub>3</sub>), 10.34 (s, 1H, -NH-).

**Example 17. 8-[4-(((4-Carboxy)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (24)**

A suspension of 20 mg of compound **21** (0.0385 mmole) in 1 mL of 1 N NaOH solution was stirred for 2 hours to turn to a clear solution. The mixture was neutralized by adding 1 mL of 1 N HCl solution. The precipitate was collected by filtration, and purified by low pressure (C18) column chromatography using linear gradient elution of 1 M triethylammonium acetate buffer (pH=7.0) and CH<sub>3</sub>CN (90/10 to 40/60) to afford 10 mg of compound **24**. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.01 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.84 (s, 2H, -

OCH<sub>2</sub>-), 7.14 (d, 2H,  $J = 8.8$  Hz, Ar), 7.77 (d, 2H,  $J = 8.8$  Hz, Ar), 7.92 (d, 2H,  $J = 8.8$  Hz, Ar), 8.09 (d, 2H,  $J = 8.8$  Hz, Ar), 10.45 (s, 1H, -NH-).

**Example 18. 8-[4-(((4-Cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-**  
5 **(n-propyl)xanthine (27)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.86 and 4.01 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.13 (d, 2H,  $J = 8.8$  Hz, Ar), 7.80 (d, 2H,  $J = 7.8$  Hz, Ar), 7.84 (d, 2H,  $J = 7.8$  Hz, Ar), 8.09 (d, 2H,  $J = 8.8$  Hz, Ar), 10.58 (s, 1H, -NH-).

10

**Example 19. 8-[4-(((4-Nitro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-**  
**(n-propyl)xanthine (28)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.89 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 7.91 (d, 2H,  $J = 8.8$  Hz, Ar), 8.10 (d, 2H,  $J = 8.8$  Hz, Ar), 8.26 (d, 2H,  $J = 8.8$  Hz, Ar), 10.76 (s, 1H, -NH-).

15

**Example 20. 8-[4-(((4-**  
**Trifluoromethyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-**

20 **propyl)xanthine (29)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 7.71 (d, 2H,  $J = 7.8$  Hz, Ar), 7.87 (d, 2H,  $J = 7.8$  Hz, Ar), 8.09 (d, 2H,  $J = 8.8$  Hz, Ar), 10.51 (s, 1H, -NH-).

25

**Example 21. 8-[4-(((4-Fluoro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-**  
**(n-propyl)xanthine (30)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.79 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 7.19 (d, 2H,  $J = 8.8$  Hz, Ar), 7.66 (dd, 2H,  $J = 5.9, 8.8$  Hz, Ar), 8.10 (d, 2H,  $J = 8.8$  Hz, Ar), 10.20 (s, 1H, -NH-).

30

**Example 22. 8-[4-(((4-Chloro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (31)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.80 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 7.8 Hz, Ar), 7.39 (d, 2H, *J* = 7.8 Hz, Ar), 7.68 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 7.8 Hz, Ar), 10.27 (s, 1H, -NH-).

**Example 23. 8-[4-(((4-Bromo)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (32)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.80 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.52 (d, 2H, *J* = 8.8 Hz, Ar), 7.63 (d, 2H, *J* = 8.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.27 (s, 1H, -NH-).

**Example 24. 8-[4-(((4-Iodo)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (33)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.79 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 7.8 Hz, Ar), 7.49 (d, 2H, *J* = 7.8 Hz, Ar), 7.68 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 7.8 Hz, Ar), 10.24 (s, 1H, -NH-).

**Example 25. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-di-(n-propyl)xanthine N',N'-[(1,2-Dimethyl)maleyl]hydrazide (34)**

<sup>1</sup>H NMR (CDCl<sub>3</sub>). 1.01 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.72 and 1.89 (2m, 4H, 2x-CH<sub>2</sub>-), 2.05 (s, 6H, 2x-CH<sub>3</sub>), 4.02 and 4.17 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 6.67 (d, 1H, *J* = 15.6 Hz, -CH=), 7.63 (d, 2H, *J* = 8.8 Hz, Ar), 7.74 (d, 1H, *J* = 15.6 Hz, -CH=), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 9.43 (s, 1H, -NH-).

**Example 26. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(n-propyl)xanthine (35)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.76 (2m, 4H, 2x-CH<sub>2</sub>-), 3.88 and 4.04 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.79 (d, 3H, *J* = 4.9 Hz, -COCH<sub>3</sub>), 6.93 (d, 1H, *J* = 15.6 Hz, -CH=), 7.51 (d, 1H, *J* = 15.6

Hz, -CH=), 7.57 (t, 1H,  $J = 7.8$  Hz, Ar), 7.69 (t, 1H,  $J = 7.8$  Hz, Ar), 7.75 (d, 2H,  $J = 7.8$  Hz, Ar), 8.03 (d, 2H,  $J = 7.8$  Hz, Ar), 8.18 (d, 2H,  $J = 7.8$  Hz, Ar), 8.53 (t, 1H,  $J = 5.8$  Hz, -NH-).

5 **Example 27. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(cyclohexylmethyl)xanthine (36)**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ). 1.02-1.27 (m, 8H, c-Hex.), 1.45-1.72 (m, 14H, c-Hex.), 4.00 and 4.08 (2d, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.96 (d, 3H,  $J = 3.9$  Hz, -COCH<sub>3</sub>), 6.66 (d, 1H,  $J = 15.6$  Hz, -CH=), 6.86 (bs, 1H, -NH-), 7.54 (t, 2H,  $J =$   
10 7.8 Hz, Ar), 7.64-7.78 (m, 3H, -CH= and Ar), 8.06 (d, 2H,  $J = 7.8$  Hz, Ar), 8.24 (d, 2H,  $J = 8.8$  Hz, Ar).

**Example 28. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-dibenzylxanthine (37)**

15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ) 4.79 (d, 3H,  $J = 5.8$  Hz, -COCH<sub>3</sub>), 5.13 (s, 2H, -NCH<sub>2</sub>-), 5.27 (s, 2H, -NCH<sub>2</sub>-), 6.93 (d, 1H,  $J = 15.6$  Hz, -CH=), 7.24-7.41 (m, 10H, 2x-Ph), 7.46 (d, 1H,  $J = 15.6$  Hz, -CH=), 7.57 (t, 1H,  $J = 8.8$  Hz, Ar), 7.69 (t, 1H,  $J = 7.8$  Hz, Ar), 7.75 (d, 2H,  $J = 8.8$  Hz, Ar), 8.03 (d, 2H,  $J = 7.8$  Hz, Ar), 8.20 (d, 2H,  $J = 7.8$  Hz, Ar), 8.54 (t, 1H,  $J = 5.8$  Hz, -NH-).

20

**Example 29. 8-[4-(((2-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-dibenzyl-xanthine (38)**

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ) 4.68 (s, 3H, -COCH<sub>3</sub>), 4.71 (s, 2H, -OCH<sub>2</sub>-), 5.12 (s, 2H, -NCH<sub>2</sub>-), 5.26 (s, 2H, -NCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 7.23-7.42  
25 (m, 10H, 2x-Ph), 7.55 (t, 1H,  $J = 7.8$  Hz, Ar), 7.68 (t, 1H,  $J = 7.8$  Hz, Ar), 8.02 (d, 2H,  $J = 7.8$  Hz, Ar), 8.11 (d, 2H,  $J = 8.8$  Hz, Ar), 8.48 (t, 1H,  $J = 4.8$  Hz, -NH-).

30 **Example 30. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-Acetylhydrazide (41)**

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 1.88 (s, 3H, CH<sub>3</sub>CO-), 3.87 and 4.02 (2t, 4H,  $J = 6.8$  Hz,

2x-NCH<sub>2</sub>-), 4.68 (s, 2H, -OCH<sub>2</sub>-), 7.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.08 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*<sup>+</sup>) 443.

**Example 31. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
5 ***N*-[(3-Carboxy)-*n*-propionyl]hydrazide (42)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 2.43 (m, 4H, -COCH<sub>2</sub>CH<sub>2</sub>CO-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.67 (s, 2H, -OCH<sub>2</sub>-), 7.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.08 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*<sup>+</sup>) 501.

10

**Example 32. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N,N*-Succinylhydrazide (43)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 2.81 (s, 4H, CH<sub>2</sub>CH<sub>2</sub>), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*<sup>+</sup>) 483.

15

**Example 33. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N,N*-[(2*S*)-Trifluoroacetamido)succinyl]hydrazide (44)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 2.70-2.90 (m, 2H, -CH<sub>2</sub>-), 3.81 and 3.98 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.69 (s, 2H, -OCH<sub>2</sub>-), 4.95 (s, 1H, -CH-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*<sup>+</sup>) 594.

20

**Example 34. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
25 ***N,N*-[(2-Phenyl)glutaryl]hydrazide (45)**

<sup>1</sup>H NMR (CDCl<sub>3</sub>). 1.05 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.75 and 1.90 (2m, 4H, 2x-CH<sub>2</sub>-), 2.3-2.5 and 2.8-3.1 (m, 5H, -CH- and 2x-CH<sub>2</sub>-), 4.04 and 4.12 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.70-4.90 (m, 2H, -OCH<sub>2</sub>-), 6.6 (d, 2H, *J* = 8.8 Hz, Ar), 7.08 (m, 2H, -Ph), 7.43 (m, 5H, -Ph and Ar); MS-FAB (*M* + *H*<sup>+</sup>) 573.

30

**Example 35. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Citraconylhydrazide (46)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 2.07 (s, 3H, CH<sub>3</sub>), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.86 (s, 2H, -OCH<sub>2</sub>-), 6.83 (s, 1H, =CH-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 495.

**Example 36. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(1,2-Dimethyl)maleylhydrazide (47)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 1.97 (s, 6H, 2x-CH<sub>3</sub>), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.86 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 509.

**Example 37. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine *N,N*-(1,2-Dimethyl)maleylhydrazide (48)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.91 (t, 3H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.73 (m, 2H, -CH<sub>2</sub>-), 1.97 (s, 6H, 2x-CH<sub>3</sub>), 3.96 (t, 2H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar); MS-EI (M<sup>+</sup>) 509, Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O<sub>6</sub> 466.1601; Found 466.1580.

**Example 38. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(2-Phenyl)maleylhydrazide (49)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.91 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.51 (s, 1H, =CH-), 7.55-7.57 (m, 3H, -Ph), 8.04-8.06 (m, 2H, -Ph), 8.11 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 557.

**Example 39. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(1,2-Diphenyl)maleylhydrazide (50)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.94 (s, 2H,

-OCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 7.45 (bs, 10H, 2x-Ph), 8.10 (d, 2H,  $J = 8.8$  Hz, Ar); MS-FAB ( $M + H^+$ ) 633.

**Example 40. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
5 ***N*-[2-((1-Carboxy)-*cis*-4-cyclohexene)-carbonyl]hydrazide (51)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 2.30-2.50 (m, 4H, 2x-CH<sub>2</sub>-), 2.80-2.95 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.66 (s, 2H, -OCH<sub>2</sub>-), 5.63 (s, 2H, 2 x =CH-), 7.09 (d, 2H,  $J = 8.8$  Hz, Ar), 8.06 (d, 2H,  $J = 8.8$  Hz, Ar); MS-  
10 FAB ( $M + H^+$ ) 553.

**Example 41. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N,N*-(*cis*-1,2,3,6-Tetrahydrophthaloyl)hydrazide (52)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
15 (2m, 4H, 2x-CH<sub>2</sub>-), 2.20-2.50 (m, 4H, 2x-CH<sub>2</sub>-), 3.56 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.66 (s, 2H, -OCH<sub>2</sub>-), 5.89 (s, 2H, 2 x =CH-), 7.09 (d, 2H,  $J = 8.8$  Hz, Ar), 8.06 (d, 2H,  $J = 8.8$  Hz, Ar); MS-FAB ( $M + H^+$ ) 535.

20 **Example 42. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N*-[2-((1-Carboxy)-1-cyclopentene)-carbonyl]hydrazide (53)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 1.87 (m, 2H, -CH<sub>2</sub>-), 2.70 (m, 4H, 2x-CH<sub>2</sub>-), 3.83 and 3.90 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.71 (s, 2H, -OCH<sub>2</sub>-), 7.09 (d, 2H,  $J = 8.8$   
25 Hz, Ar), 8.06 (d, 2H,  $J = 8.8$  Hz, Ar); MS-FAB ( $M + H^+$ ) 539.

**Example 43. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N,N*-(1-Cyclopentene-1,2-dicarbonyl)hydrazide (54)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H,  $J = 7.8$  Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
30 (2m, 4H, 2x-CH<sub>2</sub>-), 2.40 (m, 2H, -CH<sub>2</sub>-), 2.67 (4H, m, 2x-CH<sub>2</sub>-), 3.81 and 3.98 (2t, 4H,  $J = 6.8$  Hz, 2x-NCH<sub>2</sub>-), 4.85 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H,  $J = 8.8$  Hz, Ar), 8.1 (d, 2H,  $J = 8.8$  Hz, Ar); MS-FAB ( $M + H^+$ ) 521.

**Example 44. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[2-((1-Carboxy)-1-cyclohexene)-carbonyl]hydrazide (55)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 (m, 6H, 3x-CH<sub>2</sub>-), 1.74 (m, 2H, -CH<sub>2</sub>-), 2.27 (m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.68 (s, 2H, -OCH<sub>2</sub>-), 7.09 (d, 2H, *J* = 8.8 Hz, Ar), 8.06 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 553.

**Example 45. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(3,4,5,6-Tetrahydrophthaloyl)hydrazide (56)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 (m, 2H, -CH<sub>2</sub>-), 1.72 (m, 6H, 3x-CH<sub>2</sub>-), 2.30 (m, 4H, 2x-CH<sub>2</sub>-), 3.83 and 3.90 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.86 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.12 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 535.

**Example 46. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Phthaloylhydrazide (57)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.75 (s, 2H, -OCH<sub>2</sub>-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.57 (m, 4H, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 531

**Example 47. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Glutarylhydrazide (58)**

<sup>1</sup>H NMR (CDCl<sub>3</sub>). 1.05 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.75 and 1.90 (2m, 4H, 2x-CH<sub>2</sub>-), 2.10-2.30 (m, 2H, -CH<sub>2</sub>-), 2.80-3.10 (m, 4H, 2x-CH<sub>2</sub>-), 4.05 and 4.16 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.80 (s, 2H, -OCH<sub>2</sub>-), 6.75 (d, 2H, *J* = 8.8 Hz, Ar), 7.70 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 497.

**Example 48. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(3-Hydroxy)glutarylhydrazide (59)**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2x-CH<sub>2</sub>-), 2.70-3.10 (m, 4H, 2x-CH<sub>2</sub>-), 3.87 and 4.03 (2t, 4H, *J* = 6.8



Hz, -NCH<sub>2</sub>-), 4.21 (bs, 1H, -CHOH-), 4.77 (s, 2H, -OCH<sub>2</sub>-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.1 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + H<sup>+</sup>) 513.

**Example 49. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
**5 *N*-[(4-Carboxy-(2*S*)-Trifluoroacetamido)-*n*-butanoyl]hydrazide (60)**

A mixture of compound **4f** (10 mg, 0.025 mmol), 7.6 mg of L-N-Boc-glutamic acid 5-*tert*-butyl ester (0.025 mmole), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred for 8 hours at 25°C. The DMF was removed by nitrogen  
10 stream. The residue was washed with 1 mL of 1 M NaHCO<sub>3</sub> solution and dried overnight. The crude product was suspended in 0.5 mL of CHCl<sub>3</sub> and 0.5 mL of TFA added. After stirring for 30 minutes at 25°C, the mixture was concentrated to dryness and dried under high vacuum. The residue was dissolved in 0.5 mL of TFAA and the solution was stirred for 30 minutes at  
15 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC (CHCl<sub>3</sub>:MeOH=10:1) to afford 6 mg of compound **60** as a white solid (yield 40%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2*x*-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, -CH<sub>2</sub>-), 1.90-2.30 (m, 4H, 2*x*-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2*x*-NCH<sub>2</sub>-), 4.12 (m, 1H, -CH-), 4.68 (s, 2H, -OCH<sub>2</sub>-), 7.08 (d, 2H, *J* = 8.8 Hz, Ar), 8.06 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB  
20 (*M* + H<sup>+</sup>) 626.

**Example 50. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine**  
***N,N*-((2*S*)-Trifluoroacetamido)glutaryl]hydrazide (61)**

25 A mixture of compound **60** (10 mg, 0.016 mmol), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred overnight at 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC (CHCl<sub>3</sub>:MeOH=10:1) to afford 5 mg of compound **61** as a white solid (yield  
30 53%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2*x*-CH<sub>3</sub>), 1.59 and 1.73 (2m, 4H, 2*x*-CH<sub>2</sub>-), 1.90-2.30 (m, 4H, 2*x*-CH<sub>2</sub>-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2*x*-NCH<sub>2</sub>-), 4.81 (s, 2H, -OCH<sub>2</sub>-), 4.18 (m, 1H, -CH-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.1 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + H<sup>+</sup>) 608.

**Example 51. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine  
*N*-(*N*-*tert*-Butoxycarbonyl-L-leuciny)hydrazide (62)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (m, 13H, 2x-CH<sub>3</sub> and (CH<sub>3</sub>)<sub>2</sub>CH-), 1.35 (s, 9H, Boc), 1.42 (m, 2H, -CH<sub>2</sub>-), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 3.85 and 4.0  
5 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.12 (m, 1H, -CH-), 4.64 (s, 2H, -OCH<sub>2</sub>-), 7.06  
(d, 2H, *J* = 8.8 Hz, Ar), 8.05 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 614.

**Example 52. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine  
*N*-(*N*-*tert*-Butoxycarbonyl-L-methionyl)hydrazide (63)**

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.25 (m, 2H,  
-CH<sub>2</sub>-), 1.37 (s, 9H, Boc), 1.58 and 1.74 (2m, 4H, 2x-CH<sub>2</sub>-), 1.88 (m, 2H, -  
CH<sub>2</sub>-), 2.03 (s, 3H, -SCH<sub>3</sub>), 3.81 and 3.98 (2t, 4H, *J* = 6.8 Hz, 2x-NCH<sub>2</sub>-), 4.15  
(m, 1H, -CH-), 4.68 (s, 2H, -OCH<sub>2</sub>-), 7.03 (d, 2H, *J* = 8.8 Hz, Ar), 8.03 (d, 2H,  
*J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 632.

15

**Example 53. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine  
*N*-(*N*-Benzyloxycarbonyl-glycylglyciny)hydrazide (64)**

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH<sub>3</sub>), 1.58 and 1.74  
(2m, 4H, 2x-CH<sub>2</sub>-), 3.67 (m, 1H, -CH<sub>2</sub>- in glycine), 3.81 (m, 3H, -NCH<sub>2</sub>- and -  
20 CH<sub>2</sub>- in glycine), 3.98 (t, 2H, *J* = 6.8 Hz, -NCH<sub>2</sub>-), 4.64 (s, 2H, -OCH<sub>2</sub>-),  
5.03(s, 2H, -OCH<sub>2</sub>-Ph), 7.03 (d, 2H, *J* = 8.8 Hz, Ar), 7.3-7.5 (m, 5H, -Ph), 8.03  
(d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (M + H<sup>+</sup>) 649.

25 **Example 54. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine  
Methyl Ester (65)**

To a suspension of 3.2 g of 2,5-dioxo-4-amino-3-propyl tetrahydro  
pyrimidine, **66** [prepared according to the method described in Papesch *et al.*,  
*J. Org. Chem.*, 16, 1879-1890 (1951)] (18.9 mmole), 1.5 mL of glacial acetic  
acid and 3.4 mL of 6 N HCl in 50 mL of water was added dropwise a solution  
30 of 1.38 g of sodium nitrite (20 mmole) in 5 mL of water at 0°C. The mixture  
was stirred for 1 hour and the pink precipitate was collected by filtration to  
afford 3.17 g of nitro-amine, **67** (yield 78%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 0.87 (t, 3H,

$J = 7.8$  Hz,  $-\text{CH}_3$ ), 1.51 (m, 2H,  $-\text{CH}_2-$ ), 3.72 (t, 2H,  $J = 6.8$  Hz,  $-\text{NCH}_2-$ ), 9.12 (s, 1H,  $-\text{NH}_2$ ).

0.086 g of nitro-amine, **67** (0.4 mmole) was hydrogenated with 10% Pd/C in 5 mL of MeOH under  $\text{H}_2$  atmosphere (1 atm) at  $25^\circ\text{C}$  until the pink color disappeared (30 min). After the removal of the balloon of  $\text{H}_2$ , 5 mL of DMF was added and the mixture was stirred for 10 min and filtered through a Celite bed.

To the solution of crude diamine, **68** was added 0.078 g of methyl 4-formylphenoxyacetate (0.4 mmole) and 0.5 mL of acetic acid. The mixture was heated at  $50^\circ\text{C}$  for 30 min, evaporated under reduced pressure and suspended in 20 mL of ether. The yellow precipitate (mixture of **69** and **65**) was collected by filtration, dissolved in 5 mL of DMF and treated with 1 mL of aqueous solution of 0.085 g of sodium periodate (0.4 mmole) for 2 hours. After evaporation, the product was purified by crystallization in MeOH/ $\text{H}_2\text{O}$  to afford 0.048 g of xanthine, **65** (yield 34%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ). 0.90 (t, 3H,  $J = 7.8$  Hz,  $-\text{CH}_3$ ), 1.72 (m, 2H,  $-\text{CH}_2-$ ), 3.71 (s, 3H,  $-\text{OCH}_3$ ), 3.95 (t, 2H,  $J = 6.8$  Hz,  $-\text{NCH}_2-$ ), 4.89 (s, 2H,  $-\text{OCH}_2-$ ), 7.08 (d, 2H,  $J = 8.8$  Hz, Ar), 8.05 (d, 2H,  $J = 8.8$  Hz, Ar), 11.07 (s, 1H,  $-\text{NH}$ ); MS-EI ( $\text{M}^+$ ) 358, Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_5$  358.1277; Found 358.1269.

**Example 55. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine Hydrazide (**70**)**

A solution of 0.05 g of xanthine **65** (0.14 mmole) and 0.5 mL of hydrazine anhydrous in 2 mL of dry DMF was heated overnight at  $50^\circ\text{C}$ . After evaporation, the residue was suspended in MeOH and the white precipitate was collected by filtration to give 0.025 g of **70** (yield 50%). m.p. =  $267^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ). 0.90 (t, 3H,  $J = 7.8$  Hz,  $-\text{CH}_3$ ), 1.72 (m, 2H,  $-\text{CH}_2-$ ), 3.71 (s, 3H,  $-\text{OCH}_3$ ), 3.95 (t, 2H,  $J = 6.8$  Hz,  $-\text{NCH}_2-$ ), 4.34 (bs, 2H,  $\text{NH}_2$ ), 4.56 (s, 2H,  $-\text{OCH}_2-$ ), 7.08 (d, 2H,  $J = 8.8$  Hz, Ar), 8.05 (d, 2H,  $J = 8.8$  Hz, Ar), 9.39 (s, 1H,  $-\text{NH}$ ); MS-EI ( $\text{M}^+$ ) 358, Calcd. for  $\text{C}_{16}\text{H}_{18}\text{N}_6\text{O}_4$  358.1389; Found 358.1389.

Table 5 contains data for yields and characterization of the xanthine compounds of the invention. Table 6 contains data for elemental analysis of the xanthine compounds of the invention.

Table 5. The yields and chemical characterization of xanthine derivatives.

Compound	%yield	m.p.(°C)	MS	Formula	Analysis
7	13	>310	EI:482	C <sub>27</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub>	HRMS <sup>a</sup>
10	40	>310	FAB:479	C <sub>28</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub>	C,H,N
12	71	301-302	CI:462	C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>	C,H,N
13	41	268	CI:476	C <sub>26</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	C,H,N
14	46	269-270	EI:551	C <sub>32</sub> H <sub>33</sub> N <sub>5</sub> O <sub>4</sub>	C,H,N
15	55	230	EI:565	C <sub>33</sub> H <sub>35</sub> N <sub>5</sub> O <sub>4</sub>	C,H,N
16	49	215	FAB:476	C <sub>26</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	C,H,N
17	13	225	CI:558	C <sub>27</sub> H <sub>35</sub> N <sub>5</sub> O <sub>8</sub>	C,H,N
18	68	294	EI:503	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	C,H,N
19	29	269-270	EI:503	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	HRMS <sup>a</sup>
20	29	309-310	EI:503	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub> •0.23H <sub>2</sub> O	C,H,N
21	56	>310	CI:520	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>6</sub>	C,H,N
22	19	>310	CI:505	C <sub>26</sub> H <sub>28</sub> N <sub>6</sub> O <sub>5</sub>	C,H,N
23	45	>310	FAB:519	C <sub>27</sub> H <sub>30</sub> N <sub>6</sub> O <sub>5</sub> •1.8CH <sub>2</sub> Cl <sub>2</sub>	C,H,N
24	51	>310	FAB:506	C <sub>26</sub> H <sub>27</sub> N <sub>5</sub> O <sub>6</sub> •0.60CH <sub>2</sub> Cl <sub>2</sub>	C,H,N
27	44	>310	CI:487	C <sub>26</sub> H <sub>26</sub> N <sub>6</sub> O <sub>4</sub>	C,H,N
28	31	307	CI:507	C <sub>25</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub> •0.43CH <sub>3</sub> OH	C,H,N
29	44	>310	CI:530	C <sub>26</sub> H <sub>26</sub> F <sub>3</sub> N <sub>5</sub> O <sub>4</sub> •0.26CH <sub>3</sub> OH	C,H,N
30	48	298	CI:480	C <sub>25</sub> H <sub>26</sub> FN <sub>5</sub> O <sub>4</sub>	C,H,N
31	31	309	CI:496	C <sub>25</sub> H <sub>26</sub> ClN <sub>5</sub> O <sub>4</sub> •0.26(CH <sub>3</sub> ) <sub>2</sub> CO	C,H,N
32	36	>310	CI:540	C <sub>25</sub> H <sub>26</sub> BrN <sub>5</sub> O <sub>4</sub>	C,H,N
33	13	>310	CI:588	C <sub>25</sub> H <sub>26</sub> IN <sub>5</sub> O <sub>4</sub> •0.60CH <sub>3</sub> OH	C,H,N
4c	79	>310	FAB:509	C <sub>25</sub> H <sub>28</sub> N <sub>6</sub> O <sub>6</sub>	C,H,N
34	49	302-303	EI:504	C <sub>26</sub> H <sub>28</sub> N <sub>6</sub> O <sub>5</sub>	C,H,N
35	42	281-283	CI:500	C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub> •0.27MeOH	C,H,N
36	33	305	FAB:608	C <sub>36</sub> H <sub>41</sub> N <sub>5</sub> O <sub>4</sub>	HRMS <sup>a</sup>
37	76	308-309	CI:596	C <sub>36</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub> •0.60H <sub>2</sub> O	C,H,N
38	18	284	EI:599	C <sub>35</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	HRMS <sup>a</sup>

a) High-resolution mass in EI or FAB<sup>+</sup> mode (*m/z*) determined to be within acceptable limits: 7: calcd, 482.1590; found, 482.1597, 19: calcd, 503.2169; found, 503.2169, 36: calcd, 608.3237; found, 608.3251; 38: calcd, 599.2169; found, 599.2171.

Table 6. Elemental Analysis of Xanthine Derivatives

Compound No.	Formula	MW (anhyd)	Calculated (% or HRMS)	Found (% or HRMS)
7	C <sub>27</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub>	482.49	482.1590	482.1597
10	C <sub>28</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub>	478.50	C70.28, H4.63, N11.70	C70.16, H4.72, N11.72
12	C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>	461.52	C65.06, H5.90, N 15.17	C65.04, H5.93, N15.20
13	C <sub>26</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	475.54	C65.66, H6.15, N14.72	C65.70, H6.22, N14.72
14	C <sub>32</sub> H <sub>33</sub> N <sub>5</sub> O <sub>4</sub>	551.64	C69.67, H6.03, N12.69	C69.60, H6.08, N12.66
15	C <sub>33</sub> H <sub>35</sub> N <sub>5</sub> O <sub>4</sub>	565.67	C70.06, H6.24, N12.38	C70.01, H6.33, N12.35
16	C <sub>26</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	475.54	C65.66, H6.15, N14.72	C65.45, H6.23, N14.68
17	C <sub>27</sub> H <sub>35</sub> N <sub>5</sub> O <sub>8</sub>	557.60	C58.15, H6.33, N12.56	C57.93, H6.38, N12.41
18	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	503.55	C64.40, H5.81, N13.90	C64.24, H5.83, N13.87
19	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	503.55	503.2169	503.2169
20	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	503.55	C64.40, H5.81, N13.90	
	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub> •0.23H <sub>2</sub> O	507.70	C63.88, H5.85, N13.79	C63.74, H5.77, N13.80
21	C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>6</sub>	519.55	C62.41, H5.63, N13.48	C62.58, H5.67, N13.36
22	C <sub>26</sub> H <sub>28</sub> N <sub>6</sub> O <sub>5</sub>	504.54	C61.89, H5.59, N16.65	C60.64, H5.66, N15.58
23	C <sub>27</sub> H <sub>30</sub> N <sub>6</sub> O <sub>5</sub>	518.57	C62.53, H5.83, N16.20	
	C <sub>27</sub> H <sub>30</sub> N <sub>6</sub> O <sub>5</sub> •1.80CH <sub>2</sub> Cl <sub>2</sub>	671.45	C51.51, H5.04, N12.51	C51.75, H4.92, N12.77
24	C <sub>26</sub> H <sub>27</sub> N <sub>5</sub> O <sub>6</sub>	505.53	C61.77, H5.38, N13.85	
	C <sub>26</sub> H <sub>27</sub> N <sub>5</sub> O <sub>6</sub> •0.60CH <sub>2</sub> Cl <sub>2</sub>	556.49	C57.41, H5.11, N12.58	C57.12, H5.18, N12.46
27	C <sub>26</sub> H <sub>26</sub> N <sub>6</sub> O <sub>4</sub>	486.53	C64.18, H5.39, N17.27	C64.27, H5.47, N17.03
28	C <sub>25</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub>	506.51	C59.28, H5.17, N16.59	
	C <sub>25</sub> H <sub>26</sub> N <sub>6</sub> O <sub>6</sub> •0.43CH <sub>3</sub> OH	520.30	C58.70, H5.37, N16.15	C58.63, H5.26, N15.98
29	C <sub>26</sub> H <sub>26</sub> F <sub>3</sub> N <sub>5</sub> O <sub>4</sub>	529.51	C58.97, H4.95, N13.22	
	C <sub>26</sub> H <sub>26</sub> F <sub>3</sub> N <sub>5</sub> O <sub>4</sub> •0.26CH <sub>3</sub> OH	537.85	C58.64, H5.07, N13.02	C58.74, H5.07, N12.96
30	C <sub>25</sub> H <sub>26</sub> FN <sub>5</sub> O <sub>4</sub>	479.51	C62.62, H5.47, N14.60	C62.39, H5.49, N14.31
31	C <sub>25</sub> H <sub>26</sub> ClN <sub>5</sub> O <sub>4</sub>	495.96	C60.54, H5.28, N14.12	
	C <sub>25</sub> H <sub>26</sub> ClN <sub>5</sub> O <sub>4</sub> •0.26(CH <sub>3</sub> ) <sub>2</sub> CO	511.07	C60.59, H5.44, N13.70	C60.59, H5.40, N13.62
32	C <sub>25</sub> H <sub>26</sub> BrN <sub>5</sub> O <sub>4</sub>	540.41	C55.56, H4.85, N12.95	C55.28, N4.89, N12.70
33	C <sub>25</sub> H <sub>26</sub> IN <sub>5</sub> O <sub>4</sub>	587.41	C51.11, H4.46, N11.92	
	C <sub>25</sub> H <sub>26</sub> IN <sub>5</sub> O <sub>4</sub> •0.60CH <sub>3</sub> OH	606.64	C50.68, H4.72, N11.54	C50.48, H4.40, N11.28
4c	C <sub>25</sub> H <sub>28</sub> N <sub>6</sub> O <sub>6</sub>	508.53	C59.04, H5.55, N16.52	C58.79, H5.50, N16.48
34	C <sub>26</sub> H <sub>28</sub> N <sub>6</sub> O <sub>5</sub>	504.54	C61.89, H5.59, N16.65	C62.18, H5.86, N16.31
35	C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	499.56	C67.31, H5.85, N14.01	
	C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub> •0.27MeOH	508.22	C66.81, H5.97, N13.78	C66.73, H5.87, N13.61
36	C <sub>36</sub> H <sub>41</sub> N <sub>5</sub> O <sub>4</sub>	607.75	608.3237 (M+H)	608.3251
37	C <sub>36</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub>	595.65	C72.59, H4.91, N11.75	
	C <sub>36</sub> H <sub>29</sub> N <sub>5</sub> O <sub>4</sub> •0.60H <sub>2</sub> O	606.47	C71.30, H5.02, N11.55	C71.48, H4.98, N11.45
38	C <sub>35</sub> H <sub>29</sub> N <sub>5</sub> O <sub>5</sub>	599.64	599.2169	599.2171

**Example 56 Prevention of Myocardial Necrosis Following Ninety Minute LAD Occlusion by 8-[4-(((4-Cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27).**

The compounds of the invention were tested for their ability to block  
5 A<sub>2B</sub> receptors to show that mast cell degranulation can be reduced or prevented. In addition, this example shows that these antagonists could prevent or markedly attenuate the extent of myocardial infarction that occurred during coronary artery occlusion.

The left anterior descending (LAD) coronary artery of a group of dogs  
10 was isolated and encircled with a snare occluder. The dogs LAD artery blood supply was occluded for 90 minutes. The test solutions were administered intracoronary beginning immediately prior to the 90 minute occlusion interval and continued for two hours post-reperfusion (Figure 6). One group of three dogs were administered a solution containing the (4-cyano)phenyl compound,  
15 prepared in Example 18, infused at a concentration of 200nM at a rate of 1.0 mL /min. by intracoronary (i.c.) infusion into the LAD. A second group of four dogs were administered a solution containing the vehicle (carrier). Regional myocardial blood flow was measured at baseline, during LAD occlusion and for 2 hrs after reperfusion using radiolabeled microspheres  
20 (mic).

The results are illustrated in Figures 7 and 8. These figures show that the infusion of the test compound during the 90 minute occlusion dramatically attenuated infarct size compared with dogs that were untreated.

**25 Example 57 Specific binding of tritiated 8-[4-(((4-cyano)phenyl)-carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27).**

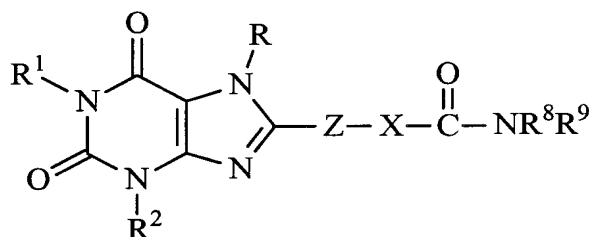
The compounds of the invention were tested for their specific binding at A<sub>2B</sub> receptors. Compound 27, 8-[4-(((4-cyano)phenylcarbamoylmethyl)-oxy]phenyl]-1,3-di-(n-propyl)xanthine was tritiated by New England Nuclear.  
30 The tritiated compound was used in radioligand binding assays on rat bladder membranes as described hereinabove substituting rat bladder cells for the cultured cells. The results show that specific binding (483 fmol/mg protein) with a K<sub>D</sub> of 1.82 nM of the test compound in the tissue was detected.

The results are illustrated in Figure 9. This is a plot of the bound test compound vs. the unbound test compound. The graph shows both specific and nonspecific binding.

5           All patents, patent applications, books and literature cited in the  
specification are hereby incorporated by reference in their entirety. In the case  
of any inconsistencies, the present disclosure, including any definitions therein  
will prevail. The invention has been described with reference to various  
specific and preferred embodiments and techniques. However, it should be  
10 understood that many variations and modifications may be made while  
remaining within the spirit and scope of the invention.

## WHAT IS CLAIMED IS:

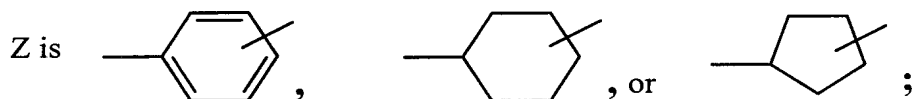
1. A compound of formula I:



I

5

wherein R, and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



- 10 X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—,

- 15 R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl; wherein R<sup>2</sup> is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —COOH and —SO<sub>3</sub>H,

- 20 wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and



wherein  $R^8$  is hydrogen,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ;  
or

$R^8$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

$R^8$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; and

wherein  $R^9$  is  $-NR^{10}R^{11}$ , or  $R^9$  is  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or

$R^9$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

$R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,

—CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H, and

wherein R<sup>10</sup> and R<sup>11</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
(C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle,  
5 heteroaryl, —C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)CR<sup>21</sup>=CR<sup>22</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>12</sup>,  
—C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl or —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkenyl, each  
optionally substituted with one or more substituents, wherein the substituents  
independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl,  
(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>,  
10 —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and  
the nitrogen atom can be taken together to form a heterocyclic ring or a  
heteroaryl ring, each ring optionally substituted with one or more substituents,  
wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
15 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN,  
—NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; wherein n is 1 to 6, and m is 0  
to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl,  
20 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
heterocycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more  
substituents independently selected from the group consisting of oxo,  
(C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
25 heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
—NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;

wherein R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> are  
independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,  
(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl;

30 wherein R<sup>21</sup> and R<sup>22</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
(C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl;

provided that —NR<sup>8</sup>R<sup>9</sup> is not aminoalkyl, aminodialkyl or hydrazino;

and

provided that when R and R<sup>8</sup> are both H, and R<sup>1</sup> and R<sup>2</sup> are both alkyl, R<sup>9</sup> is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or a pharmaceutically acceptable salt thereof.

5

2. The compound according to claim 1, wherein R and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or heteroaryl;

10 X is (C<sub>1</sub>-C<sub>6</sub>)alkylene, (C<sub>2</sub>-C<sub>6</sub>)alkenylene, (C<sub>2</sub>-C<sub>6</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—;

R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or a heterocycle;

15 wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl groups; and

20 wherein R<sup>8</sup> is hydrogen, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
25 —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;  
or

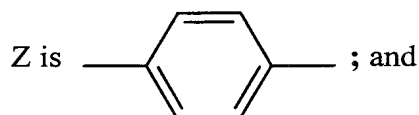
R<sup>8</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>,  
30 —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H; or

R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, substituted with one or more substituents independently selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-

- $C_6$ )alkyl,  $(C_2-C_6)$ alkenyl,  $(C_7-C_{10})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  
 $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
 $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or  
 $R^9$  is  $-NR^{10}R^{11}$ , or  $R^9$  is  $(C_3-C_6)$ cycloalkyl,  $(C_4-C_{10})$ cycloalkylalkyl,  
5  $(C_7-C_{10})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one  
or more substituents, wherein the substituents independently are oxo,  $(C_1-$   
 $C_6)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_6)$ aryl,  $(C_7-C_{10})$ aralkyl,  
heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  
 $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ;  
10 or  
 $R^9$  is  $(C_1-C_6)$ alkyl, substituted with one or more substituents  
independently selected from the group consisting of oxo,  $(C_2-C_6)$ alkenyl,  
 $(C_6)$ aryl,  $(C_7-C_{10})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  
 $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  
15  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or  
 $R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents  
independently selected from the group consisting of  $(C_1-C_6)$ alkyl, halo $(C_1-$   
 $C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_7-C_{10})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  
 $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
20  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or  
wherein  $R^{10}$  and  $R^{11}$  are independently hydrogen,  $(C_1-C_4)$ alkyl,  
 $(C_2-C_4)$ alkenyl,  $(C_3-C_6)$ cycloalkyl,  $(C_6)$ aryl,  $(C_7-C_{10})$ aralkyl, heterocycle,  
heteroaryl,  $-C(O)(CH_2)_nCO_2R^{12}$ ,  $-C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$ ,  
 $-C(O)R^{12}$ ,  $-C(O)(C_3-C_6)$ cycloalkyl or  $-C(O)(C_3-C_6)$ cycloalkenyl, each  
25 optionally substituted with one or more substituents, wherein the substituents  
independently are oxo,  $(C_1-C_6)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_6)$ alkenyl,  $(C_6)$ aryl,  
 $(C_7-C_{10})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  
 $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
 $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or the  $R^{10}$  and  $R^{11}$  groups and  
30 the nitrogen atom can be taken together to form a heterocyclic ring or a  
heteroaryl ring, each ring optionally substituted with one or more substituents,  
wherein the substituents independently are oxo,  $(C_1-C_6)$ alkyl, halo $(C_1-C_6)$ alkyl,  
 $(C_2-C_6)$ alkenyl,  $(C_6)$ aryl,  $(C_7-C_{10})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,

—NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H.

3. The compound according to claim 2, wherein R, R<sup>1</sup> and R<sup>2</sup> are  
5 independently hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl,  
(C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>6</sub>)aryl, or  
(C<sub>7</sub>-C<sub>10</sub>)aralkyl;



- X is O-(C<sub>1</sub>-C<sub>7</sub>)alkylene, O-(C<sub>2</sub>-C<sub>7</sub>)alkenylene, (C<sub>1</sub>-C<sub>8</sub>)alkylene or  
10 (C<sub>2</sub>-C<sub>8</sub>)alkenylene; wherein

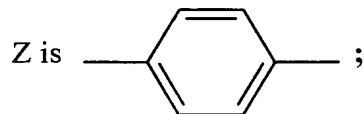
- R<sup>9</sup> is (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl,  
heterocycle or heteroaryl, each optionally substituted with one or more  
substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>6</sub>)alkyl,  
halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo,  
15 —OR<sup>15</sup>, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>,  
—N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or

- R<sup>9</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, substituted with one or more substituents  
independently selected from the group consisting of oxo, (C<sub>2</sub>-C<sub>6</sub>)alkenyl,  
(C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>,  
20 —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>,  
—SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H; or

- R<sup>9</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, substituted with one or more substituents  
independently selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-  
C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN,  
25 —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H.

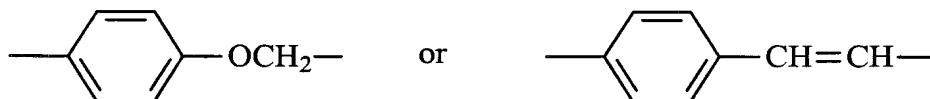
4. The compound according to claim 2, wherein R, R<sup>1</sup> and R<sup>2</sup> are  
independently hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl,

(C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>6</sub>)aryl, or (C<sub>7</sub>-C<sub>10</sub>)aralkyl;



X is O-(C<sub>1</sub>-C<sub>7</sub>)alkylene, O-(C<sub>2</sub>-C<sub>7</sub>)alkenylene, (C<sub>1</sub>-C<sub>8</sub>)alkylene or  
 5 (C<sub>2</sub>-C<sub>8</sub>)alkenylene; and  
 R<sup>9</sup> is —NR<sup>10</sup>R<sup>11</sup>.

5. The compound according to claim 3, wherein —X—Z— is



R<sup>1</sup> and R<sup>2</sup> are independently —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH=CH<sub>2</sub>,  
 10 —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> or cyclohexylmethyl.

6. The compound according to claim 5, wherein aryl is phenyl and aralkyl is benzyl.

15 7. The compound according to claim 6, wherein R<sup>9</sup> is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, benzyl, F, Cl, Br, I, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup> or —C(O)NR<sup>17</sup>R<sup>18</sup>, or

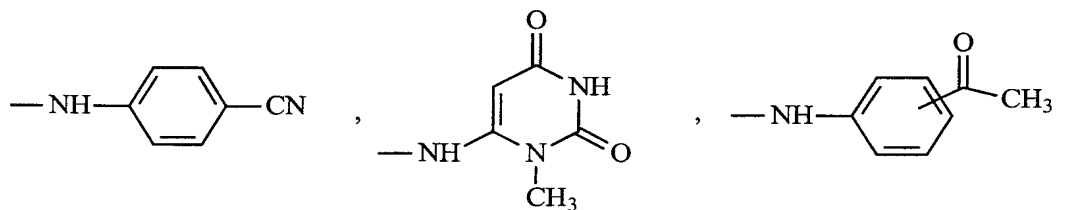
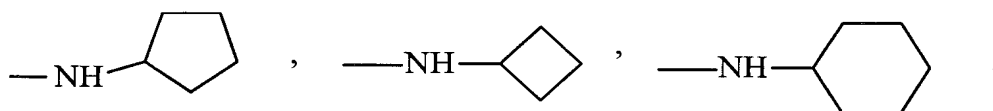
benzyl, optionally substituted with 1-3 substituents that are  
 20 independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, —OH, F, Cl, Br, I, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup> or —C(O)NR<sup>17</sup>R<sup>18</sup>.

8. The compound according to claim 7, wherein R<sup>8</sup> is hydrogen and R<sup>9</sup> is  
 25 phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I,

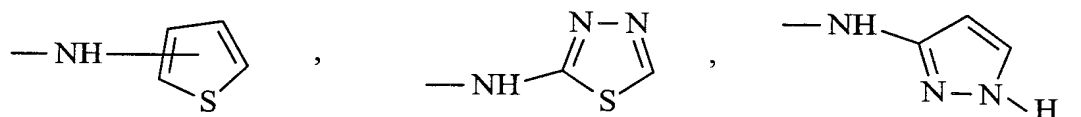
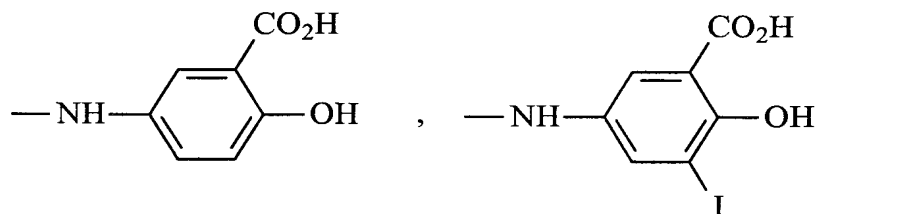
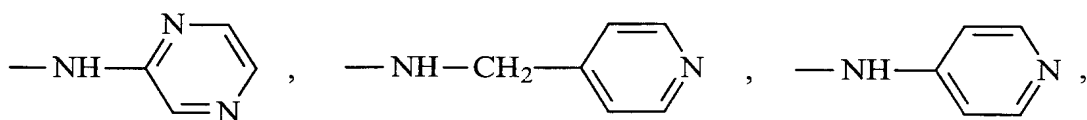
—CN, —COOH, —C(O)OCH<sub>3</sub>, —C(O)CH<sub>2</sub>CH<sub>3</sub>, —C(O)CH<sub>3</sub>, —C(O)NH<sub>2</sub> or —C(O)NHCH<sub>3</sub> or

- benzyl, optionally substituted with 1-3 substituents that are independently —CH<sub>2</sub>CH<sub>3</sub>, F, Cl, Br, I, —CN, —COOH, —CO<sub>2</sub>CH<sub>3</sub>,  
 5 —C(O)CH<sub>2</sub>CH<sub>3</sub>, —C(O)CH<sub>3</sub>, —C(O)NH<sub>2</sub> or —C(O)NHCH<sub>3</sub>.

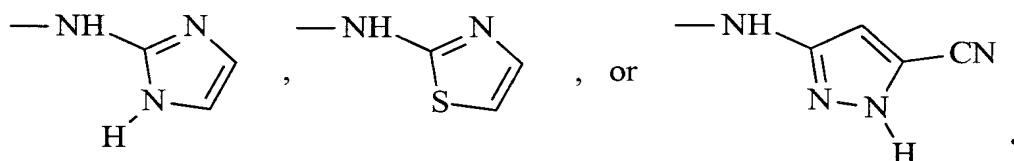
9. The compound according to claim 5, wherein —NR<sup>8</sup>R<sup>9</sup> is



10



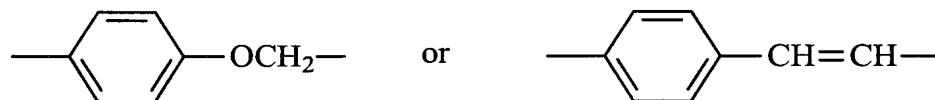
73



10. The compound according to claim 9, wherein R is H, R<sup>1</sup> and R<sup>2</sup> are each —CH<sub>2</sub>CH=CH<sub>2</sub>, and R<sup>9</sup> is 4-cyanophenyl.

5 11. The compound according to claim 9, wherein R is H, R<sup>1</sup> and R<sup>2</sup> are each —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, and R<sup>9</sup> is 3-carboxy-4-hydroxyphenyl or 3-acetylphenyl.

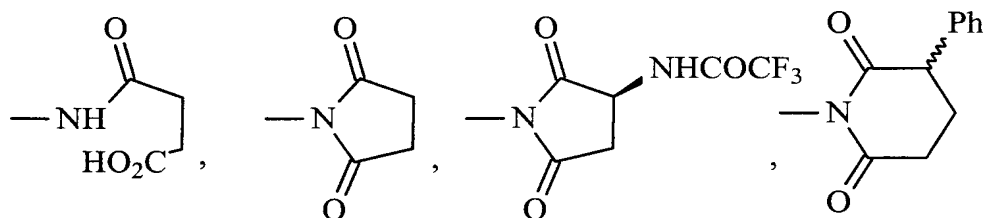
12. The compound according to claim 4, wherein —X—Z— is



10 R<sup>1</sup> and R<sup>2</sup> are independently —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH=CH<sub>2</sub>,  
—CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> or cyclohexylmethyl; and  
R<sup>8</sup> is hydrogen, aryl or aralkyl.

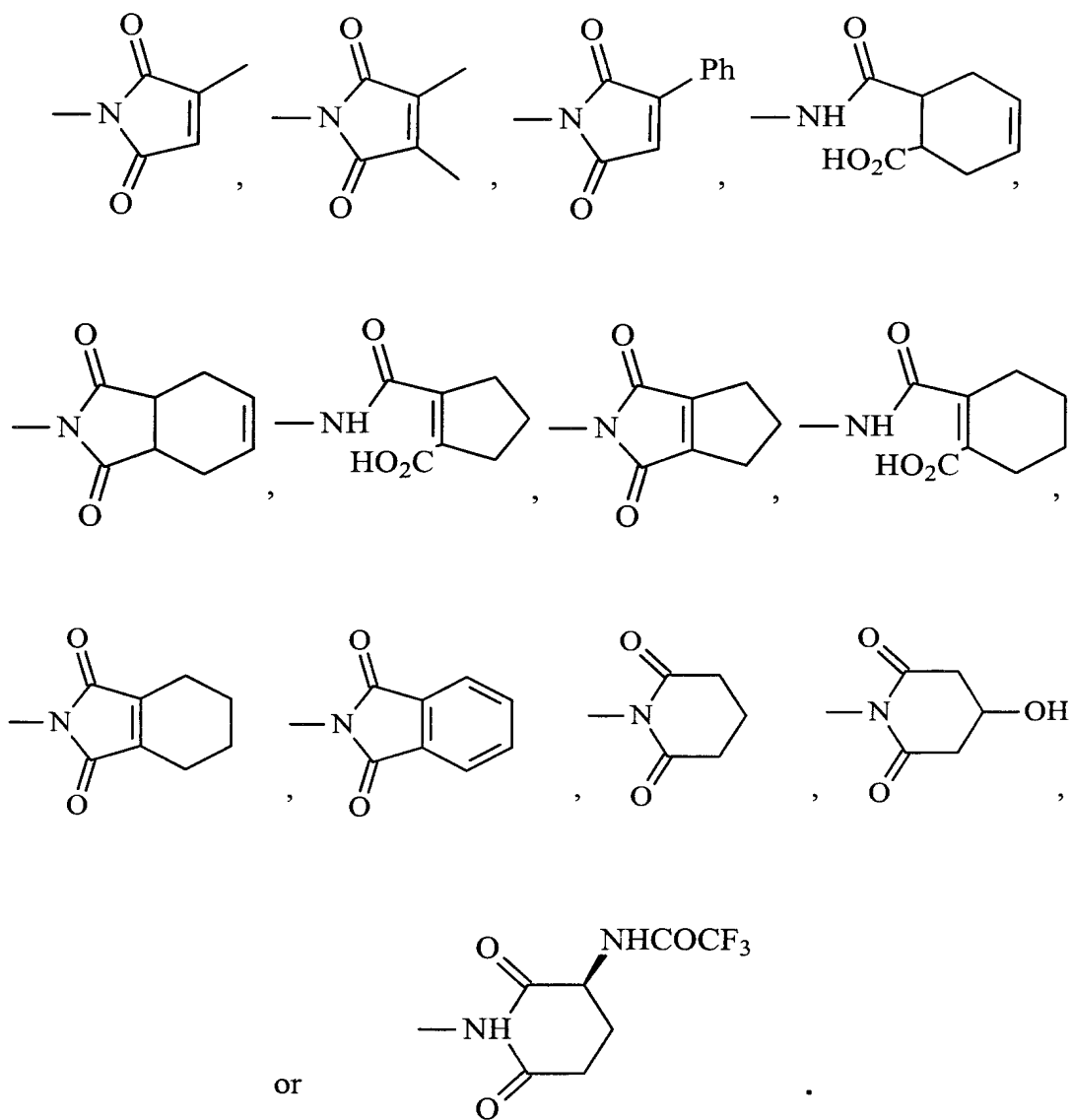
13. The compound according to claim 12, wherein R<sup>10</sup> and R<sup>11</sup> are  
15 independently hydrogen, —C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)CR<sup>21</sup>=CR<sup>22</sup>CO<sub>2</sub>R<sup>12</sup>,  
—C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, —C(O)(C<sub>3</sub>-C<sub>6</sub>)cycloalkenyl or wherein  
the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom taken together form said  
optionally substituted heterocycle or a heteroaryl ring, and n is 2.

20 14. The compound of claim 13, wherein R<sup>9</sup> is

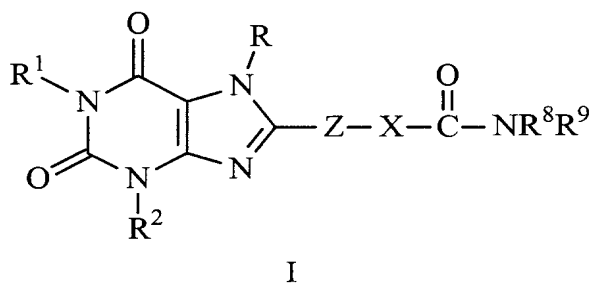




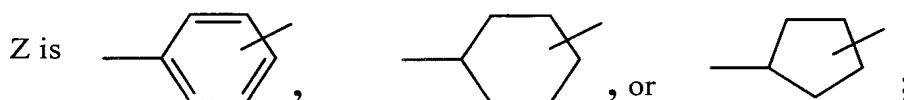
74



5 15. A compound of formula I:



wherein R and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



- 5 X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—,

- R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl; wherein R<sup>2</sup> is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —COOH and —SO<sub>3</sub>H,

- wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and

- wherein R<sup>8</sup> is hydrogen, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or

- R<sup>8</sup> is (C<sub>1</sub>-C<sub>8</sub>)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H; or

$R^8$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
 5  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; and

wherein  $R^9$  is  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl,  
 10 heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ;  
 or

$R^9$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  
 15  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

$R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  
 20  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ , and

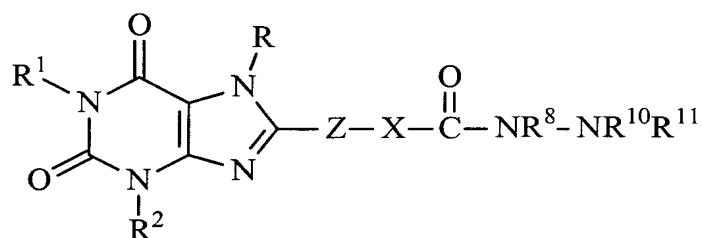
wherein,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{23}$  and  $R^{24}$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  
 25  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl;

provided that  $-NR^8R^9$  is not aminoalkyl or aminodialkyl; and

provided that when R and  $R^8$  are both H, and  $R^1$  and  $R^2$  are both alkyl,  $R^9$  is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

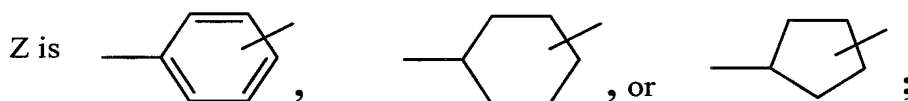
30 a pharmaceutically acceptable salt thereof.

16. A compound of formula II:



II

wherein R and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—,

R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl; wherein R<sup>2</sup> is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —COOH and —SO<sub>3</sub>H,

wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and

wherein R<sup>8</sup> is hydrogen, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-

$C_{18}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or

$R^8$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents

- 5 independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

$R^8$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents

- 10 independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; and

wherein  $R^{10}$  and  $R^{11}$  are independently hydrogen,  $(C_1-C_8)$ alkyl,

- 15  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-C(O)(CH_2)_nCO_2R^{12}$ ,  $-C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$ ,  $-C(O)R^{12}$ ,  $-C(O)(C_3-C_8)$ cycloalkyl or  $-C(O)(C_3-C_8)$ cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or the  $R^{10}$  and  $R^{11}$  groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, 25 wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; wherein n is 1 to 6, and m is 0 to 4;

- 30  $R^{12}$  is hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heterocycle, or heteroaryl,

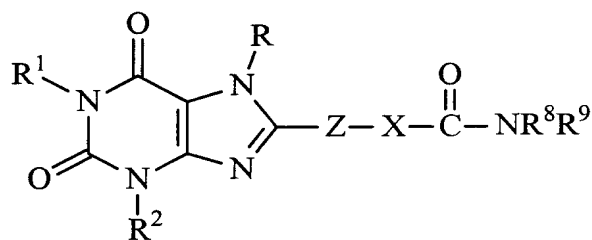
wherein the  $R^{12}$  group is optionally substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  
 5  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ;

wherein  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{23}$  and  $R^{24}$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl;

$R^{21}$  and  $R^{22}$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  
 10  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl;

provided that  $-NR^8-NR^{10}R^{11}$  is not hydrazino; or  
 a pharmaceutically acceptable salt thereof.

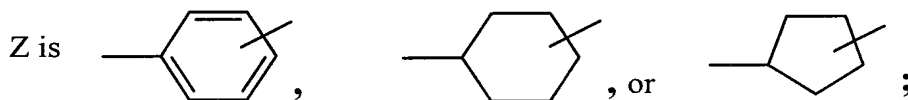
17. A pharmaceutical composition comprising a compound of formula I:  
 15



I

wherein  $R$ , and  $R^1$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl,  $(C_1-C_8)$ alkoxy,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl, heterocycle,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or heteroaryl;

20



X is  $(C_1-C_8)$ alkylene,  $(C_2-C_8)$ alkenylene,  $(C_2-C_8)$ alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula  $\text{—O—}$ ,  $\text{—N(R}^4\text{)C(O)—}$ ,  $\text{—OC(O)—}$ ,  $\text{—N(R}^5\text{)(R}^6\text{)—}$ ,  $\text{—S—}$ ,  $\text{—S(O)—}$  or  $\text{—SO}_2\text{—}$ ,

$\text{R}^2$  is hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkynyl}$ ,  $(\text{C}_1\text{—C}_8)\text{-alkoxy}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,

- 5  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl; wherein  $\text{R}^2$  is optionally substituted with one or more substituents selected from the group consisting of  $\text{—OH}$ ,  $\text{—SH}$ ,  $\text{—NH}_2$ ,  $\text{—NHR}^7$ ,  $\text{—CN}$ ,  $\text{—COOH}$  and  $\text{—SO}_3\text{H}$ ,

wherein  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are independently hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$  or

- 10  $\text{halo(C}_1\text{—C}_6\text{)alkyl}$ ; and

wherein  $\text{R}^8$  is hydrogen,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $\text{halo(C}_1\text{—C}_6\text{)alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ ,

- 15 heteroaryl, halo,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ;  
or

$\text{R}^8$  is  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , substituted with one or more substituents independently selected from the group consisting of oxo,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,

- 20  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_6\text{—C}_{10})\text{aryl}$ , substituted with one or more substituents independently selected from the group consisting of  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $\text{halo(C}_1\text{—C}_6\text{)alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,

- 25  $\text{C}_6\text{)alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; and

wherein  $\text{R}^9$  is  $\text{—NR}^{10}\text{R}^{11}$ , or  $\text{R}^9$  is  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally

- 30 substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $\text{halo(C}_1\text{—C}_6\text{)alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,

—OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>,  
—SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or

R<sup>9</sup> is (C<sub>1</sub>-C<sub>8</sub>)alkyl, substituted with one or more substituents  
independently selected from the group consisting of oxo, (C<sub>2</sub>-C<sub>8</sub>)alkenyl,  
5 (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>,  
—OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>,  
—SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H; or

R<sup>9</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, substituted with one or more substituents  
independently selected from the group consisting of (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-  
10 C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>,  
—CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H, and

wherein R<sup>10</sup> and R<sup>11</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
(C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle,  
15 heteroaryl, —C(O)(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>12</sup>, —C(O)CR<sup>21</sup>=CR<sup>22</sup>(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>R<sup>12</sup>,  
—C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl or —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkenyl, each  
optionally substituted with one or more substituents, wherein the substituents  
independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl,  
(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>,  
20 —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and  
the nitrogen atom can be taken together to form a heterocyclic ring or a  
heteroaryl ring, each ring optionally substituted with one or more substituents,  
wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
25 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN,  
—NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
—C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; wherein n is 1 to 6, and m is 0  
to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl,  
30 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
heterocycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more  
substituents independently selected from the group consisting of oxo, (C<sub>1</sub>-C<sub>8</sub>)-



alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;

wherein R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> are

- 5 independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein R<sup>21</sup> and R<sup>22</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl;

provided that —NR<sup>8</sup>R<sup>9</sup> is not aminoalkyl, aminodialkyl or

- 10 hydrazino; and

provided that when R and R<sup>8</sup> are both H, and R<sup>1</sup> and R<sup>2</sup> are both alkyl, R<sup>9</sup> is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or a pharmaceutically acceptable salt thereof in combination with a

- 15 pharmaceutically acceptable carrier.

18. The composition according to claim 17, wherein R and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or heteroaryl;

X is (C<sub>1</sub>-C<sub>6</sub>)alkylene, (C<sub>2</sub>-C<sub>6</sub>)alkenylene, (C<sub>2</sub>-C<sub>6</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—;

- 25 R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or a heterocycle;

wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl groups; and

- 30 wherein R<sup>8</sup> is hydrogen, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-

$C_6$ )alkyl, halo( $C_1$ - $C_6$ )alkyl, ( $C_2$ - $C_6$ )alkenyl, ( $C_6$ )aryl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or

5  $R^8$  is ( $C_1$ - $C_6$ )alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, ( $C_2$ - $C_6$ )alkenyl, ( $C_6$ )aryl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

10  $R^8$  is ( $C_6$ - $C_{10}$ )aryl, substituted with one or more substituents independently selected from the group consisting of ( $C_1$ - $C_6$ )alkyl, halo( $C_1$ - $C_6$ )alkyl, ( $C_2$ - $C_6$ )alkenyl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

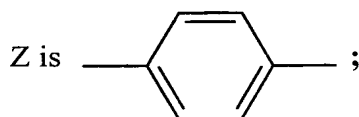
15  $R^9$  is  $-NR^{10}R^{11}$ , or  $R^9$  is ( $C_3$ - $C_6$ )cycloalkyl, ( $C_4$ - $C_{10}$ )cycloalkylalkyl, ( $C_7$ - $C_{10}$ )aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, ( $C_1$ - $C_6$ )alkyl, halo( $C_1$ - $C_6$ )alkyl, ( $C_2$ - $C_6$ )alkenyl, ( $C_6$ )aryl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  
20  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or  
or

$R^9$  is ( $C_1$ - $C_6$ )alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, ( $C_2$ - $C_6$ )alkenyl, ( $C_6$ )aryl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  
25  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

$R^9$  is ( $C_6$ - $C_{10}$ )aryl, substituted with one or more substituents independently selected from the group consisting of ( $C_1$ - $C_6$ )alkyl, halo( $C_1$ - $C_6$ )alkyl, ( $C_2$ - $C_6$ )alkenyl, ( $C_7$ - $C_{10}$ )aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  
30  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

wherein  $R^{10}$  and  $R^{11}$  are independently hydrogen, ( $C_1$ - $C_4$ )alkyl, ( $C_2$ - $C_4$ )alkenyl, ( $C_3$ - $C_6$ )cycloalkyl, ( $C_6$ )aryl, ( $C_7$ - $C_{10}$ )aralkyl, heterocycle,

- heteroaryl,  $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$ ,  $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$ ,  
 $-\text{C}(\text{O})\text{R}^{12}$ ,  $-\text{C}(\text{O})(\text{C}_3-\text{C}_6)\text{cycloalkyl}$  or  $-\text{C}(\text{O})(\text{C}_3-\text{C}_6)\text{cycloalkenyl}$ , each  
optionally substituted with one or more substituents, wherein the substituents  
independently are oxo,  $(\text{C}_1-\text{C}_6)\text{alkyl}$ , halo $(\text{C}_1-\text{C}_6)\text{alkyl}$ ,  $(\text{C}_2-\text{C}_6)\text{alkenyl}$ ,  $(\text{C}_6)\text{aryl}$ ,  
5  $(\text{C}_7-\text{C}_{10})\text{aralkyl}$ , heteroaryl,  $-\text{OR}^{15}$ , halo,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2\text{R}^{15}$ ,  
 $-\text{OC}(\text{O})\text{R}^{16}$ ,  $-\text{C}(\text{O})\text{R}^{16}$ ,  $-\text{NR}^{13}\text{R}^{14}$ ,  $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$ ,  $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$ ,  
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$ ,  $-\text{SR}^{19}$ ,  $-\text{SO}_2\text{R}^{20}$  or  $-\text{SO}_3\text{H}$ ; or the  $\text{R}^{10}$  and  $\text{R}^{11}$  groups and  
the nitrogen atom can be taken together to form a heterocyclic ring or a  
heteroaryl ring, each ring optionally substituted with one or more substituents,  
10 wherein the substituents independently are oxo,  $(\text{C}_1-\text{C}_6)\text{alkyl}$ , halo $(\text{C}_1-\text{C}_6)\text{alkyl}$ ,  
 $(\text{C}_2-\text{C}_6)\text{alkenyl}$ ,  $(\text{C}_6)\text{aryl}$ ,  $(\text{C}_7-\text{C}_{10})\text{aralkyl}$ , heteroaryl,  $-\text{OR}^{15}$ , halo,  $-\text{CN}$ ,  
 $-\text{NO}_2$ ,  $-\text{CO}_2\text{R}^{15}$ ,  $-\text{OC}(\text{O})\text{R}^{16}$ ,  $-\text{C}(\text{O})\text{R}^{16}$ ,  $-\text{NR}^{13}\text{R}^{14}$ ,  $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$ ,  
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$ ,  $-\text{SR}^{19}$ ,  $-\text{SO}_2\text{R}^{20}$  or  $-\text{SO}_3\text{H}$ .
- 15 19. The composition according to claim 18, wherein  $\text{R}$ ,  $\text{R}^1$  and  $\text{R}^2$  are  
independently hydrogen,  $(\text{C}_1-\text{C}_4)\text{alkyl}$ ,  $(\text{C}_2-\text{C}_4)\text{alkenyl}$ ,  $(\text{C}_2-\text{C}_4)\text{alkynyl}$ ,  
 $(\text{C}_1-\text{C}_4)\text{alkoxy}$ ,  $(\text{C}_5-\text{C}_6)\text{cycloalkyl}$ ,  $(\text{C}_6-\text{C}_{10})\text{cycloalkylalkyl}$ ,  $(\text{C}_6)\text{aryl}$ , or  
 $(\text{C}_7-\text{C}_{10})\text{aralkyl}$ ;



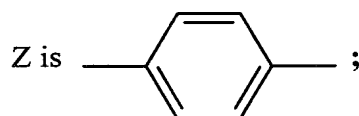
- 20 X is  $\text{O}-(\text{C}_1-\text{C}_7)\text{alkylene}$ ,  $\text{O}-(\text{C}_2-\text{C}_7)\text{alkenylene}$ ,  $(\text{C}_1-\text{C}_8)\text{alkylene}$  or  
 $(\text{C}_2-\text{C}_8)\text{alkenylene}$ ; wherein
- $\text{R}^9$  is  $(\text{C}_3-\text{C}_6)\text{cycloalkyl}$ ,  $(\text{C}_4-\text{C}_{10})\text{cycloalkylalkyl}$ ,  $(\text{C}_7-\text{C}_{10})\text{aralkyl}$ ,  
heterocycle or heteroaryl, each optionally substituted with one or more  
substituents, wherein the substituents independently are oxo,  $(\text{C}_1-\text{C}_6)\text{alkyl}$ ,  
25 halo $(\text{C}_1-\text{C}_6)\text{alkyl}$ ,  $(\text{C}_2-\text{C}_6)\text{alkenyl}$ ,  $(\text{C}_6)\text{aryl}$ ,  $(\text{C}_7-\text{C}_{10})\text{aralkyl}$ , heteroaryl, halo,  
 $-\text{OR}^{15}$ ,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2\text{R}^{15}$ ,  $-\text{OC}(\text{O})\text{R}^{16}$ ,  $-\text{C}(\text{O})\text{R}^{16}$ ,  $-\text{NR}^{13}\text{R}^{14}$ ,  
 $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$ ,  $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$ ,  $-\text{SR}^{19}$ ,  $-\text{SO}_2\text{R}^{20}$  or  $-\text{SO}_3\text{H}$ ; or
- $\text{R}^9$  is  $(\text{C}_1-\text{C}_6)\text{alkyl}$ , substituted with one or more substituents  
independently selected from the group consisting of oxo,  $(\text{C}_2-\text{C}_6)\text{alkenyl}$ ,

(C<sub>6</sub>)aryl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>,  
—OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>,  
—SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H; or

R<sup>9</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, substituted with one or more substituents

- 5 independently selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>7</sub>-C<sub>10</sub>)aralkyl, heteroaryl, halo, —OR<sup>15</sup>, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> and —SO<sub>3</sub>H.

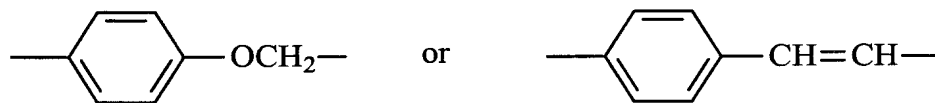
- 10 20. The composition according to claim 18, wherein R, R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)cycloalkylalkyl, (C<sub>6</sub>)aryl, or (C<sub>7</sub>-C<sub>10</sub>)aralkyl;



- 15 X is O-(C<sub>1</sub>-C<sub>7</sub>)alkylene, O-(C<sub>2</sub>-C<sub>7</sub>)alkenylene, (C<sub>1</sub>-C<sub>8</sub>)alkylene or (C<sub>2</sub>-C<sub>8</sub>)alkenylene; and

R<sup>9</sup> is —NR<sup>10</sup>R<sup>11</sup>.

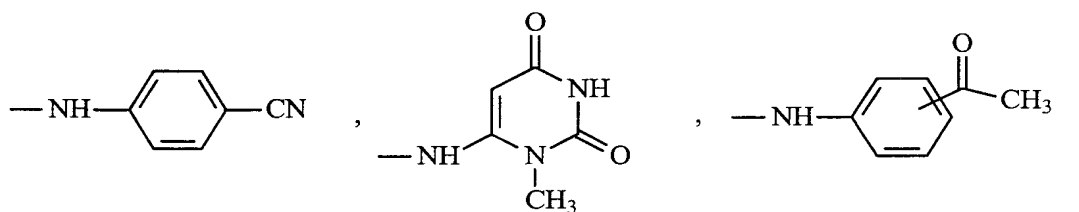
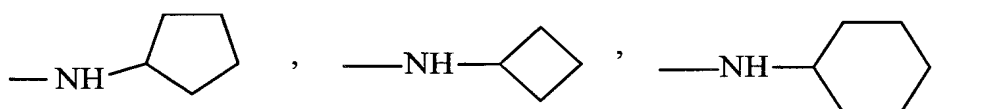
21. The composition according to claim 19, wherein —Z—X— is



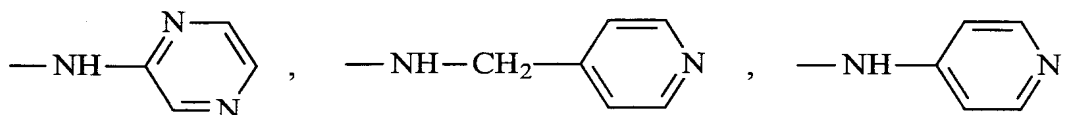
- 20 and R<sup>1</sup> and R<sup>2</sup> are independently —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH=CH<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> or cyclohexylmethyl.

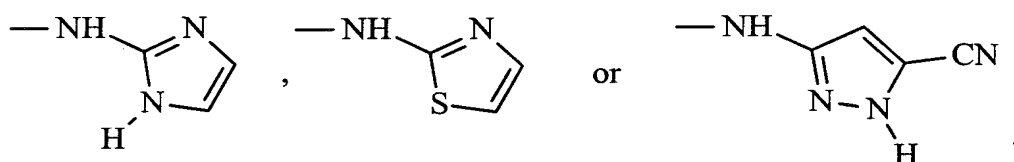
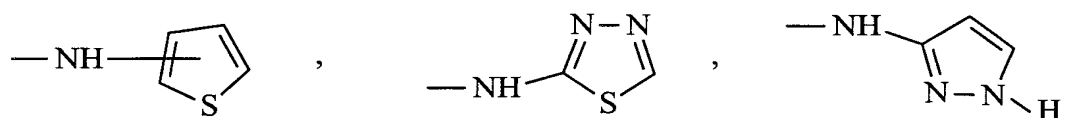
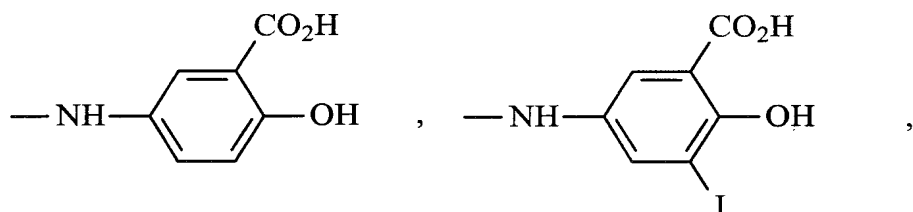
22. The composition according to claim 21, wherein wherein aryl is phenyl and aralkyl is benzyl.

23. The composition according to claim 22, wherein  $R^9$  is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl, benzyl, F, Cl, Br, I,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2R^{15}$ ,  $-\text{C(O)}R^{16}$ ,  $-\text{NR}^{13}R^{14}$  or  $-\text{C(O)}\text{NR}^{17}R^{18}$ , or
- 5 benzyl, optionally substituted with 1-3 substituents that are independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl,  $-\text{OH}$ , F, Cl, Br, I,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2R^{15}$ ,  $-\text{C(O)}R^{16}$ ,  $-\text{NR}^{13}R^{14}$  or  $-\text{C(O)}\text{NR}^{17}R^{18}$ .
- 10 24. The composition according to claim 23, wherein  $R^8$  is hydrogen and  $R^9$  is phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I,  $-\text{CN}$ ,  $-\text{COOH}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{C(O)}\text{CH}_2\text{CH}_3$ ,  $-\text{C(O)}\text{CH}_3$ ,  $-\text{C(O)}\text{NH}_2$  or  $-\text{C(O)}\text{NHCH}_3$  or
- 15 benzyl, optionally substituted with 1-3 substituents that are independently  $-\text{CH}_2\text{CH}_3$ , F, Cl, Br, I,  $-\text{CN}$ ,  $-\text{COOH}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{C(O)}\text{CH}_2\text{CH}_3$ ,  $-\text{C(O)}\text{CH}_3$ ,  $-\text{C(O)}\text{NH}_2$  or  $-\text{C(O)}\text{NHCH}_3$ .
25. The composition according to claim 21, wherein  $-\text{NR}^8R^9$  is:

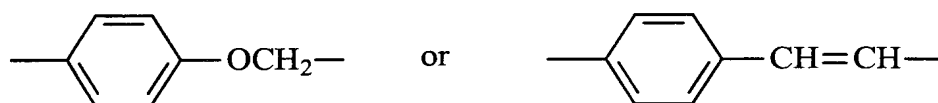


20





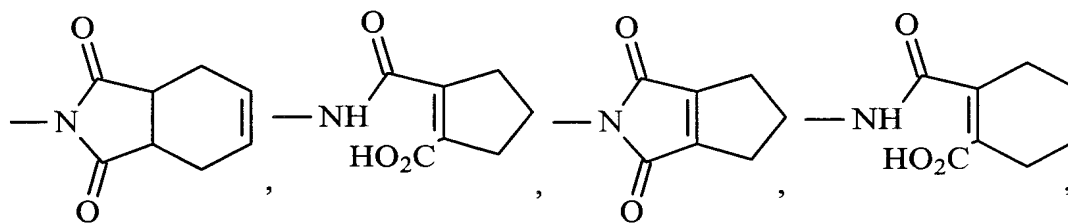
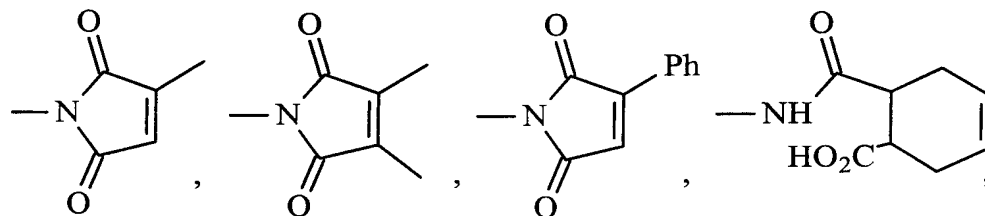
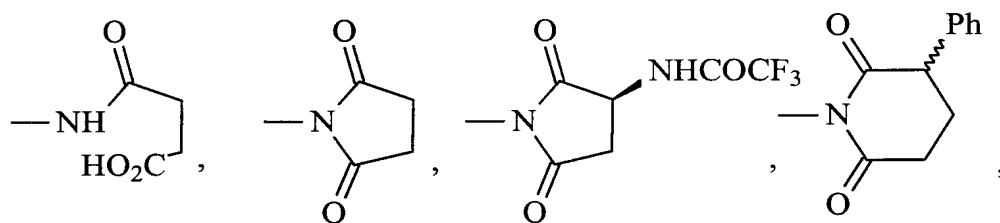
26. The composition according to claim 25, wherein  $\text{R}$  and  $\text{R}^8$  are each  $\text{H}$ ,  $\text{R}^1$  and  $\text{R}^2$  are each  $\text{—CH}_2\text{CH=CH}_2$ , and  $\text{R}^9$  is 4-cyanophenyl.
27. The composition according to claim 26, wherein  $\text{R}$  and  $\text{R}^8$  are each  $\text{H}$ ,  $\text{R}^1$  and  $\text{R}^2$  are each  $\text{—CH}_2\text{CH}_2\text{CH}_3$ , and  $\text{R}^9$  is 3-carboxy-4-hydroxyphenyl or 3-acetylphenyl.
28. The composition according to claim 20, wherein  $\text{—Z—X—}$  is



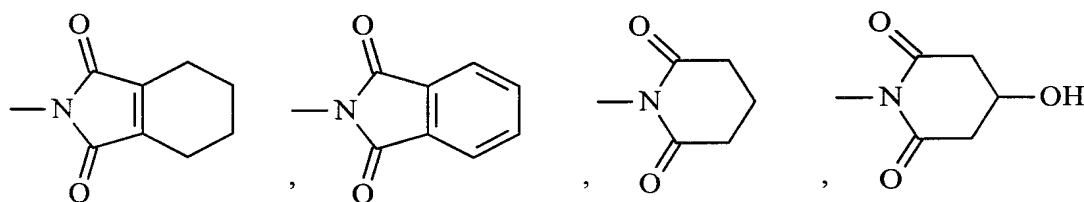
- wherein  $\text{R}^1$ , and  $\text{R}^2$  are independently  $\text{—CH}_2\text{CH}_3$ ,  $\text{—CH}_2\text{CH=CH}_2$ ,  $\text{—CH}_2\text{CH}_2\text{CH}_3$  or cyclohexylmethyl; and  $\text{R}^8$  is hydrogen, aryl or aralkyl.

29. The composition according to claim 28, wherein  $R^{10}$  and  $R^{11}$  are independently hydrogen,  $-C(O)(CH_2)_nCO_2R^{12}$ ,  $-C(O)CR^{21}=CR^{22}CO_2R^{12}$ ,  $-C(O)R^{12}$ ,  $-C(O)(C_3-C_6)cycloalkyl$ ,  $-C(O)(C_3-C_6)cycloalkenyl$  or wherein the  $R^{10}$  and  $R^{11}$  groups and the nitrogen atom taken together form said
- 5 optionally substituted heterocycle or a heteroaryl ring, and n is 2.

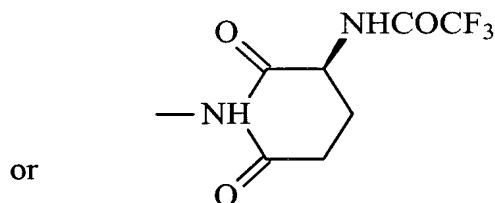
30. The composition of claim 29, wherein  $R^9$  is



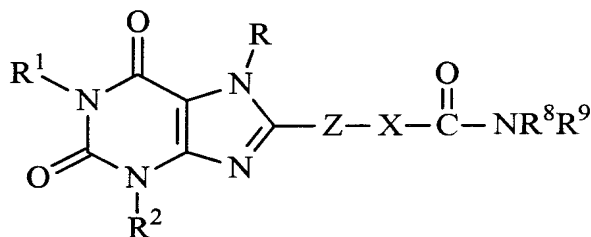
10



89

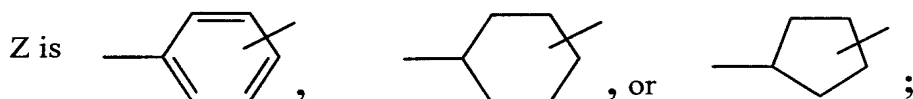


31. A pharmaceutical composition comprising a compound of formula I:



I

wherein R and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—, —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—,

R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl; wherein R<sup>2</sup> is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —COOH and —SO<sub>3</sub>H,



wherein  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl; and

- wherein  $R^8$  is hydrogen,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,   
 5  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl,  $(C_1-C_8)$ alkoxy, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl, halo,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$    
 10 or  $-SO_3H$ ; or

- $R^8$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,   
 15  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

- $R^8$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,   
 20  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; and

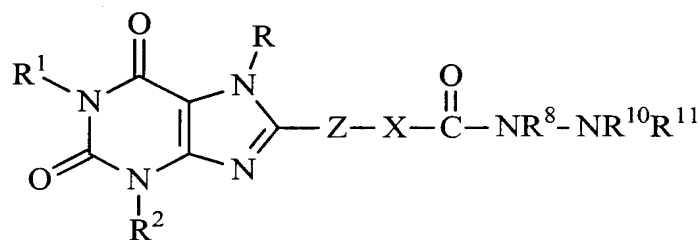
- wherein  $R^9$  is  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl,  $(C_7-C_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl,   
 25 heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  or  $-SO_3H$ ; or

- $R^9$  is  $(C_1-C_8)$ alkyl, substituted with one or more substituents independently selected from the group consisting of oxo,  $(C_2-C_8)$ alkenyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ , halo,  $-CN$ ,  $-NO_2$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  $-C(O)NR^{17}R^{18}$ ,   
 30  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ ; or

- $R^9$  is  $(C_6-C_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of  $(C_1-C_8)$ alkyl, halo $(C_1-C_6)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_7-C_{18})$ aralkyl, heteroaryl,  $-OR^{15}$ ,  $-CN$ ,  $-NO_2$ ,  $-CO_2R^{15}$ ,  $-OC(O)R^{16}$ ,  $-C(O)R^{16}$ ,  $-NR^{13}R^{14}$ ,  $-N(R^{23})C(O)R^{24}$ ,  
 5  $-C(O)NR^{17}R^{18}$ ,  $-SR^{19}$ ,  $-SO_2R^{20}$  and  $-SO_3H$ , and  
 wherein,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{23}$  and  $R^{24}$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_3-C_8)$ cycloalkyl,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or halo $(C_1-C_6)$ alkyl;  
 provided that  $-NR^8R^9$  is not aminoalkyl or aminodialkyl; and  
 10 provided that when R and  $R^8$  are both H, and  $R^1$  and  $R^2$  are both alkyl,  $R^9$  is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or  
 a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

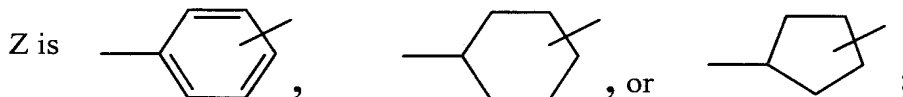
15

32. A pharmaceutical composition comprising a compound of formula II:



II

- wherein R and  $R^1$  are independently hydrogen,  $(C_1-C_8)$ alkyl,  $(C_2-C_8)$ alkenyl,  $(C_2-C_8)$ alkynyl,  $(C_1-C_8)$ alkoxy,  $(C_3-C_8)$ cycloalkyl,  $(C_4-C_{16})$ cycloalkylalkyl, heterocycle,  $(C_6-C_{10})$ aryl,  $(C_7-C_{18})$ aralkyl or heteroaryl;  
 20



X is  $(C_1-C_8)$ alkylene,  $(C_2-C_8)$ alkenylene,  $(C_2-C_8)$ alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula  $\text{—O—}$ ,  $\text{—N(R}^4\text{)C(O)—}$ ,  $\text{—OC(O)—}$ ,  $\text{—N(R}^5\text{)(R}^6\text{)—}$ ,  $\text{—S—}$ ,  $\text{—S(O)—}$  or  $\text{—SO}_2\text{—}$ ,

$\text{R}^2$  is hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkynyl}$ ,  $(\text{C}_1\text{—C}_8)\text{alkoxy}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl; wherein  $\text{R}^2$  is optionally substituted with one or more substituents selected from the group consisting of  $\text{—OH}$ ,  $\text{—SH}$ ,  $\text{—NH}_2$ ,  $\text{—NHR}^7$ ,  $\text{—CN}$ ,  $\text{—COOH}$  and  $\text{—SO}_3\text{H}$ ,

wherein  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are independently hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$  or halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ;

wherein  $\text{R}^8$  is hydrogen,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_1\text{—C}_8)\text{alkoxy}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl, halo,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , substituted with one or more substituents independently selected from the group consisting of oxo,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_6\text{—C}_{10})\text{aryl}$ , substituted with one or more substituents independently selected from the group consisting of  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23}\text{)C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; and

wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently hydrogen,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,  $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$ ,  $(\text{C}_6\text{—C}_{10})\text{aryl}$ ,  $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ , heteroaryl,  $\text{—C(O)(CH}_2\text{)}_n\text{CO}_2\text{R}^{12}$ ,  $\text{—C(O)CR}^{21}\text{=CR}^{22}\text{(CH}_2\text{)}_m\text{CO}_2\text{R}^{12}$ ,  $\text{—C(O)R}^{12}$ ,  $\text{—C(O)(C}_3\text{—C}_8)\text{cycloalkyl}$  or  $\text{—C(O)(C}_3\text{—C}_8)\text{cycloalkenyl}$ , each optionally substituted with one or more substituents, wherein the substituents independently are oxo,  $(\text{C}_1\text{—C}_8)\text{alkyl}$ , halo $(\text{C}_1\text{—C}_6)\text{alkyl}$ ,  $(\text{C}_2\text{—C}_8)\text{alkenyl}$ ,

(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>,  
 —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
 —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and  
 the nitrogen atom can be taken together to form a heterocyclic ring or a  
 5 heteroaryl ring, each ring optionally substituted with one or more substituents,  
 wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN,  
 —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>,  
 —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; wherein n is 1 to 6, and m is 0  
 10 to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl,  
 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
 heterocycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more  
 15 substituents independently selected from the group consisting of oxo,  
 (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
 heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>,  
 —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;  
 wherein R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> are

20 independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,  
 (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>21</sup> and R<sup>22</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl,  
 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl;

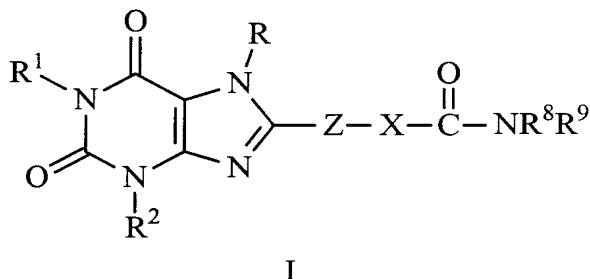
provided that —NR<sup>8</sup>—NR<sup>10</sup>R<sup>11</sup> is not hydrazino; or

25 a pharmaceutically acceptable salt thereof, in combination with a  
 pharmaceutically acceptable carrier.

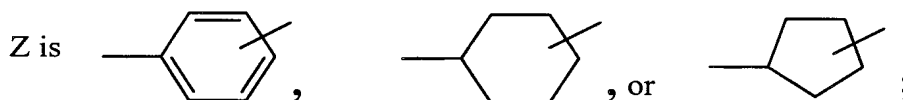
33. A method for treating asthma comprising administering an effective  
 amount of a compound of claim 1, 15 or 16 to a mammal in need of such  
 30 treatment.

34. A method for treating diarrheal diseases, insulin resistance, diabetes,  
 cancer, ischemia/reperfusion injuries, diabetic retinopathy or hyperbaric

oxygen-induced retinopathy, comprising administering an effective amount of a compound of formula I:



- wherein R, and R<sup>1</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
 5 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, heterocycle, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or heteroaryl;



- X is (C<sub>1</sub>-C<sub>8</sub>)alkylene, (C<sub>2</sub>-C<sub>8</sub>)alkenylene, (C<sub>2</sub>-C<sub>8</sub>)alkynylene, wherein  
 one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is  
 10 optionally replaced with a group having the formula —O—, —N(R<sup>4</sup>)C(O)—,  
 —OC(O)—, —N(R<sup>5</sup>)(R<sup>6</sup>)—, —S—, —S(O)— or —SO<sub>2</sub>—,

- R<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl, (C<sub>1</sub>-C<sub>8</sub>)-  
 alkoxy, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-  
 C<sub>18</sub>)aralkyl, heterocycle or heteroaryl; wherein R<sup>2</sup> is optionally substituted with  
 15 one or more substituents selected from the group consisting of —OH, —SH,  
 —NH<sub>2</sub>, —NHR<sup>7</sup>, —CN, —COOH and —SO<sub>3</sub>H,

wherein R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl,  
 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or  
 halo(C<sub>1</sub>-C<sub>6</sub>)alkyl; and

- 20 wherein R<sup>8</sup> is hydrogen, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl,  
 (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle or heteroaryl, each optionally substituted with one  
 or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-  
 C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,

heteroaryl, halo,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  
 $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ;  
 or

$\text{R}^8$  is  $(\text{C}_1\text{—C}_8)$ alkyl, substituted with one or more substituents  
 5 independently selected from the group consisting of oxo,  $(\text{C}_2\text{—C}_8)$ alkenyl,  
 $(\text{C}_6\text{—C}_{10})$ aryl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  
 $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  
 $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^8$  is  $(\text{C}_6\text{—C}_{10})$ aryl, substituted with one or more substituents  
 10 independently selected from the group consisting of  $(\text{C}_1\text{—C}_8)$ alkyl, halo $(\text{C}_1\text{—C}_6)$ alkyl,  
 $(\text{C}_2\text{—C}_8)$ alkenyl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  
 $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  
 $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; and

wherein  $\text{R}^9$  is  $\text{—NR}^{10}\text{R}^{11}$ , or  $\text{R}^9$  is  $(\text{C}_3\text{—C}_8)$ cycloalkyl,  $(\text{C}_4\text{—C}_{16})$ cyclo-  
 15 alkylalkyl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heterocycle or heteroaryl, each optionally  
 substituted with one or more substituents, wherein the substituents  
 independently are oxo,  $(\text{C}_1\text{—C}_8)$ alkyl, halo $(\text{C}_1\text{—C}_6)$ alkyl,  $(\text{C}_2\text{—C}_8)$ alkenyl,  $(\text{C}_6\text{—C}_{10})$ aryl,  
 $(\text{C}_7\text{—C}_{18})$ aralkyl, heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  $\text{—CO}_2\text{R}^{15}$ ,  
 $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  
 20  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  or  $\text{—SO}_3\text{H}$ ; or

$\text{R}^9$  is  $(\text{C}_1\text{—C}_8)$ alkyl, substituted with one or more substituents  
 independently selected from the group consisting of oxo,  $(\text{C}_2\text{—C}_8)$ alkenyl,  
 $(\text{C}_6\text{—C}_{10})$ aryl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heteroaryl,  $\text{—OR}^{15}$ , halo,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  
 $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  
 25  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ ; or

$\text{R}^9$  is  $(\text{C}_6\text{—C}_{10})$ aryl, substituted with one or more substituents  
 independently selected from the group consisting of  $(\text{C}_1\text{—C}_8)$ alkyl, halo $(\text{C}_1\text{—C}_6)$ alkyl,  
 $(\text{C}_2\text{—C}_8)$ alkenyl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heteroaryl,  $\text{—OR}^{15}$ ,  $\text{—CN}$ ,  $\text{—NO}_2$ ,  
 $\text{—CO}_2\text{R}^{15}$ ,  $\text{—OC(O)R}^{16}$ ,  $\text{—C(O)R}^{16}$ ,  $\text{—NR}^{13}\text{R}^{14}$ ,  $\text{—N(R}^{23})\text{C(O)R}^{24}$ ,  
 30  $\text{—C(O)NR}^{17}\text{R}^{18}$ ,  $\text{—SR}^{19}$ ,  $\text{—SO}_2\text{R}^{20}$  and  $\text{—SO}_3\text{H}$ , and

wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently hydrogen,  $(\text{C}_1\text{—C}_8)$ alkyl,  
 $(\text{C}_2\text{—C}_8)$ alkenyl,  $(\text{C}_3\text{—C}_8)$ cycloalkyl,  $(\text{C}_6\text{—C}_{10})$ aryl,  $(\text{C}_7\text{—C}_{18})$ aralkyl, heterocycle,  
 heteroaryl,  $\text{—C(O)(CH}_2)_n\text{CO}_2\text{R}^{12}$ ,  $\text{—C(O)CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$ ,

—C(O)R<sup>12</sup>, —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl or —C(O)(C<sub>3</sub>-C<sub>8</sub>)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>,  
 5 —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; or the R<sup>10</sup> and R<sup>11</sup> groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 10 (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H; wherein n is 1 to 6, and m is 0 to 4;

R<sup>12</sup> is hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>2</sub>-C<sub>8</sub>)alkynyl,  
 15 (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>16</sub>)cycloalkylalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl, heterocycle, or heteroaryl,

wherein the R<sup>12</sup> group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl,  
 20 heteroaryl, —OR<sup>15</sup>, halo, —CN, —NO<sub>2</sub>, —CO<sub>2</sub>R<sup>15</sup>, —OC(O)R<sup>16</sup>, —C(O)R<sup>16</sup>, —NR<sup>13</sup>R<sup>14</sup>, —N(R<sup>23</sup>)C(O)R<sup>24</sup>, —C(O)NR<sup>17</sup>R<sup>18</sup>, —SR<sup>19</sup>, —SO<sub>2</sub>R<sup>20</sup> or —SO<sub>3</sub>H;

wherein R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>23</sup> and R<sup>24</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl or halo(C<sub>1</sub>-C<sub>6</sub>)alkyl;

25 wherein R<sup>21</sup> and R<sup>22</sup> are independently hydrogen, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>8</sub>)alkenyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub>-C<sub>18</sub>)aralkyl;

or a pharmaceutically acceptable salt thereof to a mammal in need of such treatment.

30 35. A therapeutic method for preventing or treating a pathological condition or symptom in a mammal, wherein the activity of adenosine A<sub>2B</sub> receptors is implicated and antagonism of its action is desired comprising

administering to the mammal an effective amount of a compound of claim 1, 15 or 16.

36. The compound of claim 1, wherein one of the atoms of said compound  
5 is replaced by its radionuclide.

37. The compound of claim 36, wherein the radionuclide is tritium, or radioactive iodine.



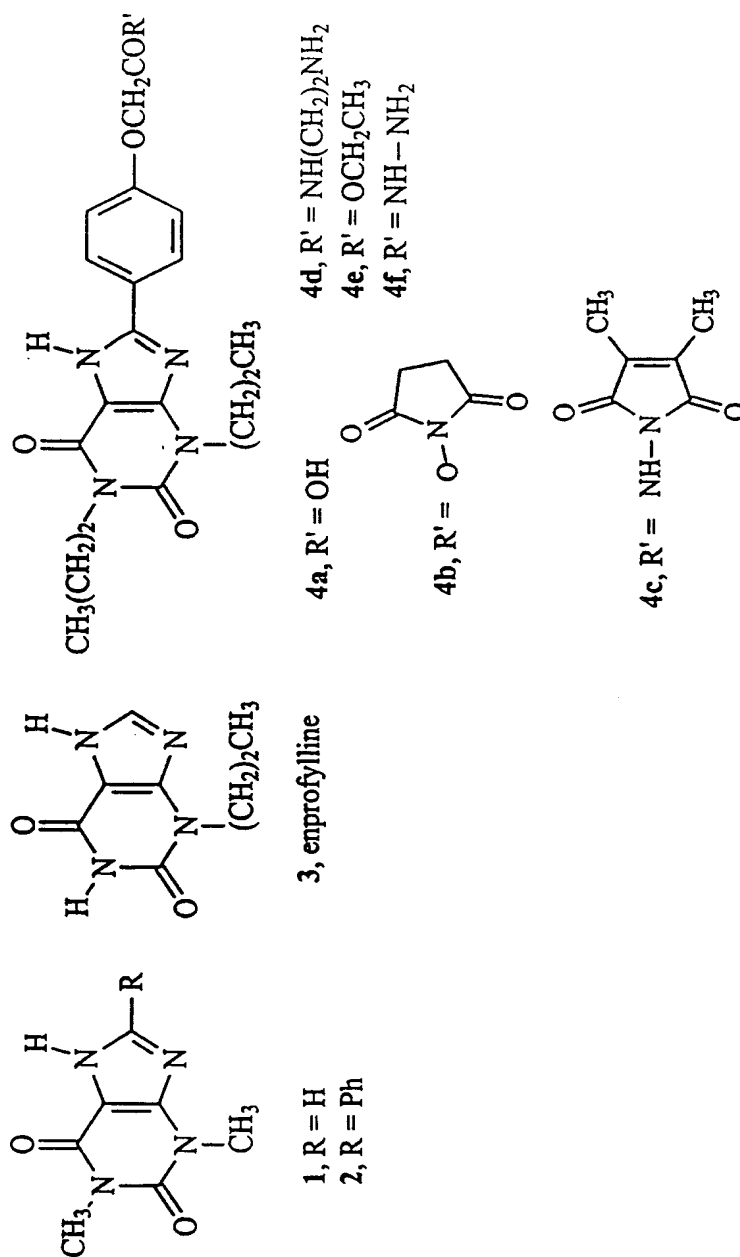


FIG. 1

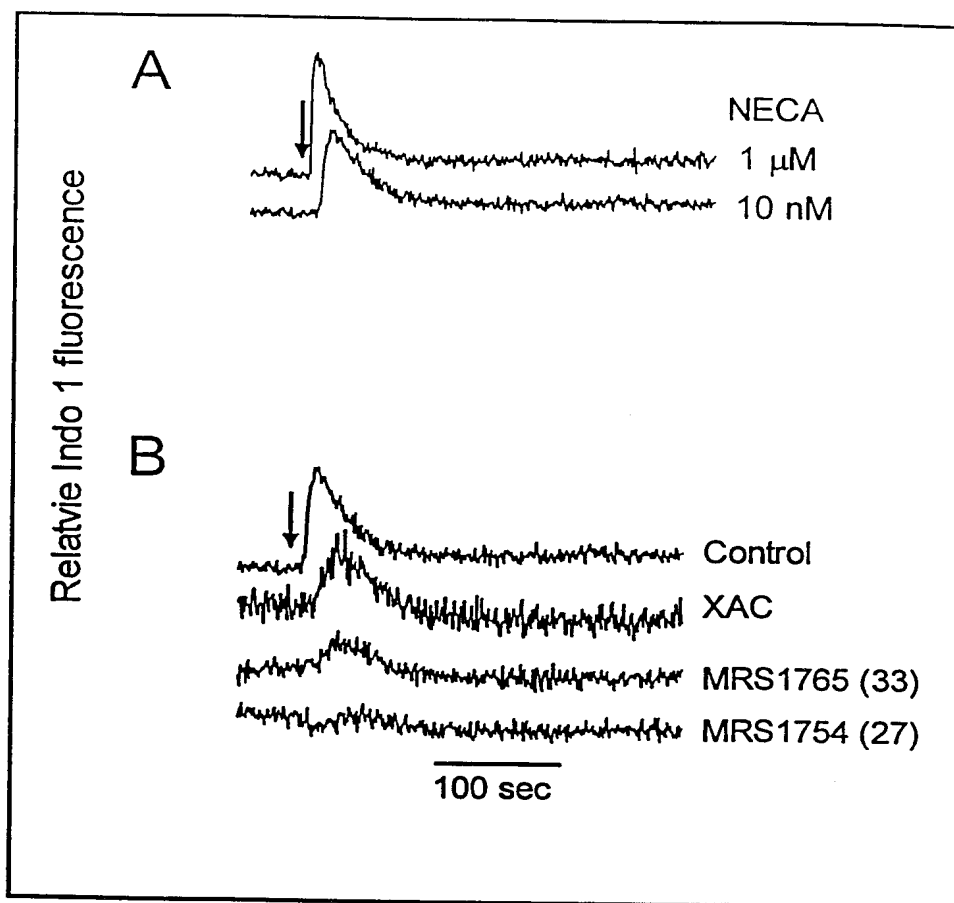
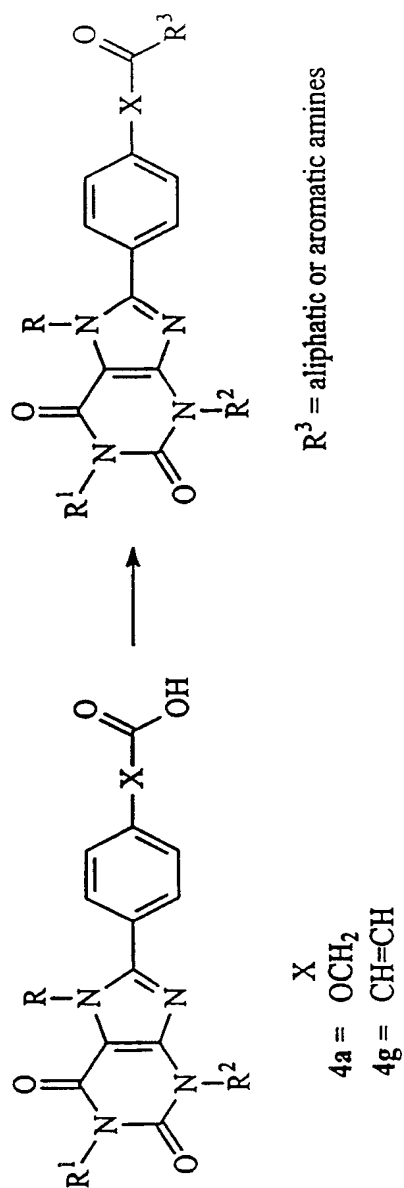


FIG. 2



Reagents: 1) EDAC, DMAP, amines in DMF/CH<sub>2</sub>Cl<sub>2</sub>; 2) BOP-Cl, triethylamine, amines in CH<sub>2</sub>Cl<sub>2</sub>; or 3) SOCl<sub>2</sub>; amines in pyridine/CH<sub>2</sub>Cl<sub>2</sub>.

FIG. 3

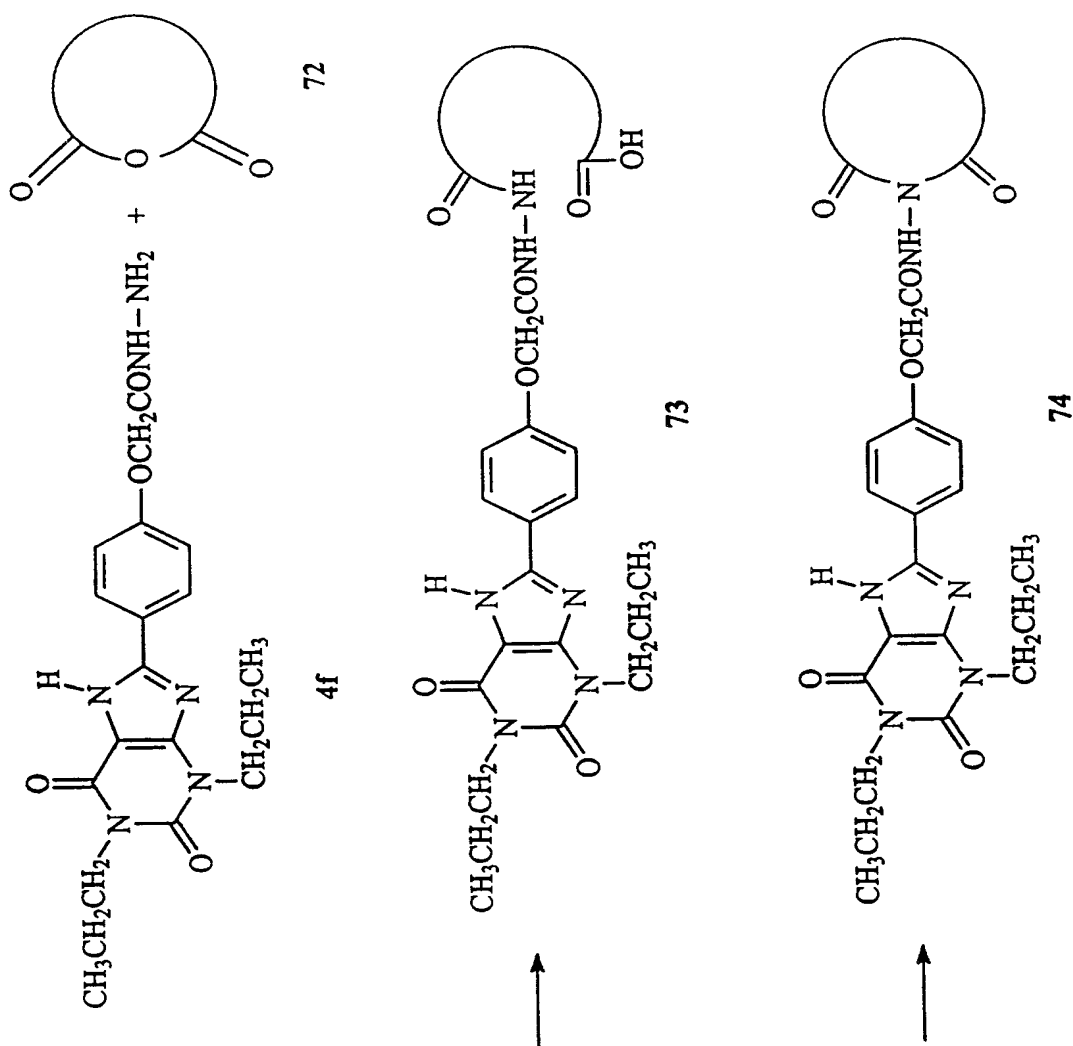


FIG. 4

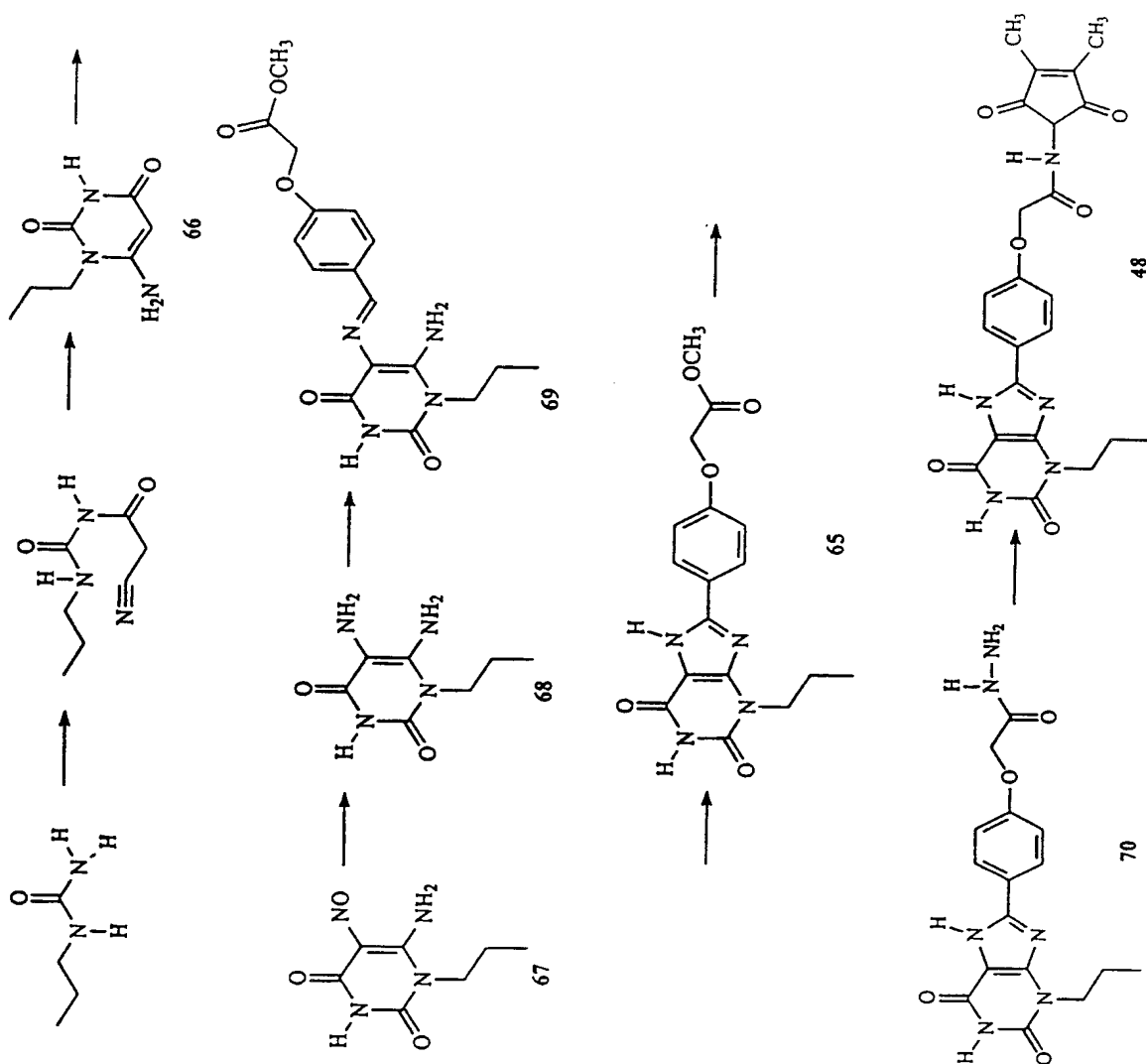
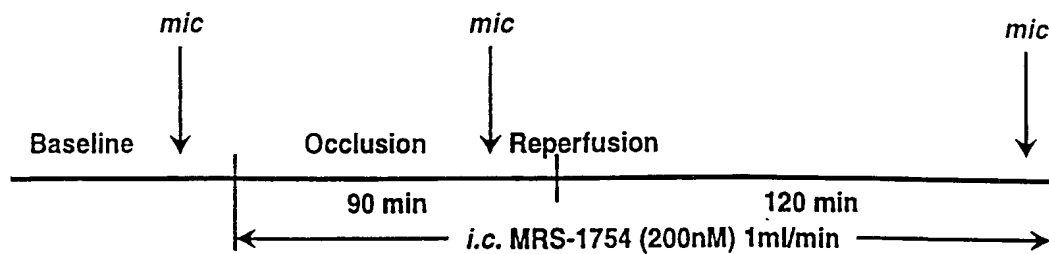
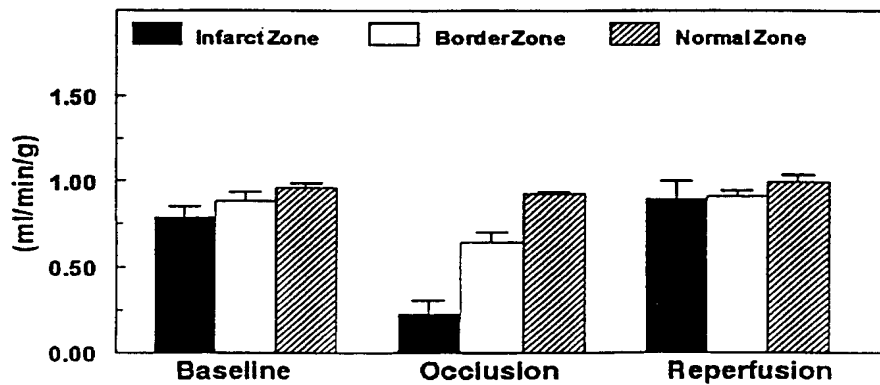


FIG. 5

6 / 8

**Blood Sampling from CS**

Baseline (x 2), 30 sec, 60 sec, 90 sec, 2 min, 3 min, 5 min, 10 min, 15 min, 30 min

**FIG. 6****FIG. 7**

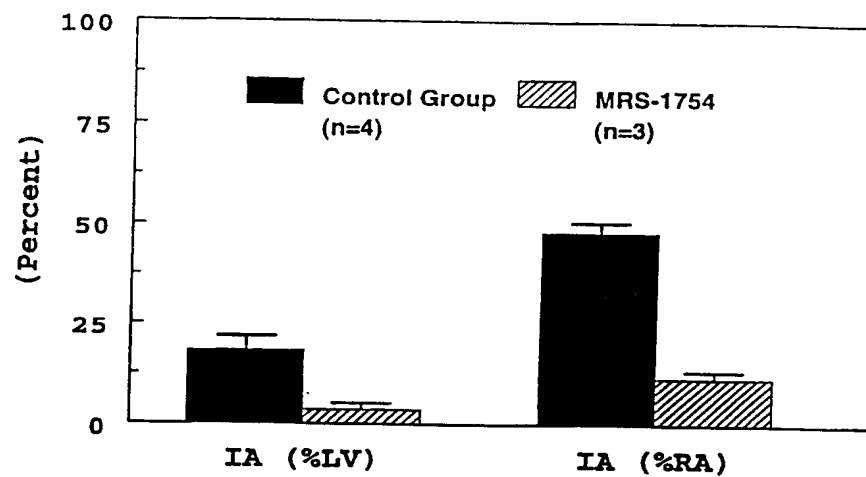
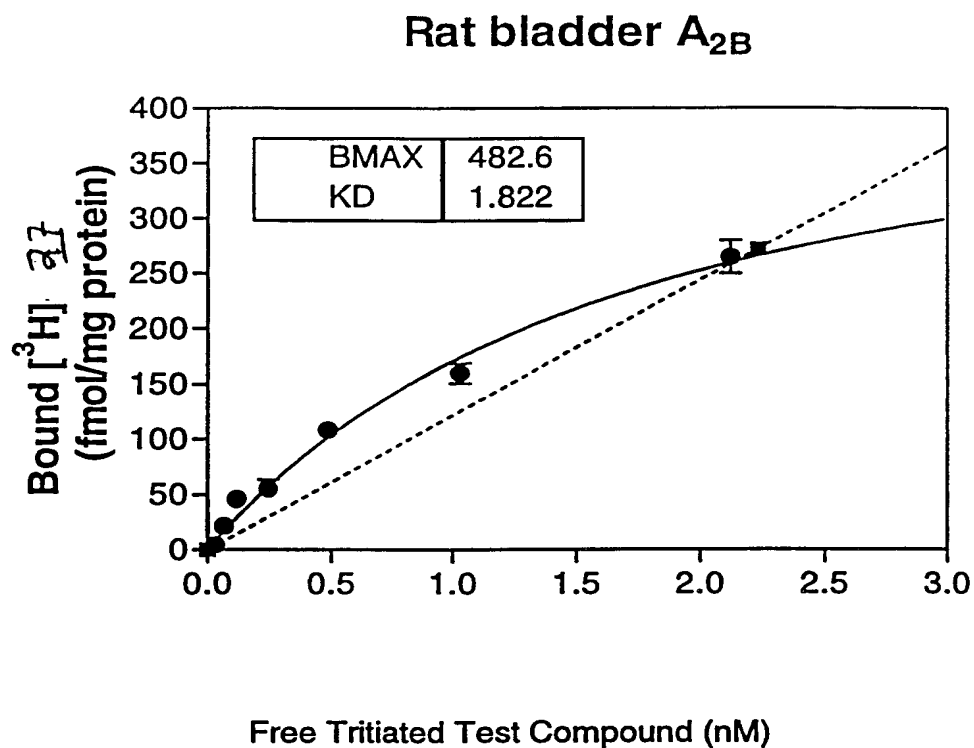


FIG. 8



[<sup>3</sup>H] 8-[4-(((4-Cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27).

----- Specific binding (•).  
----- Nonspecific binding.

**FIG. 9**